AN OVERVIEW OF SYNDROMIC OROFACIAL CLEFT IN COMBINED CLEFT CLINIC UNIVERSITI MALAYA FROM 2000 - 2020

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AN OVERVIEW OF SYNDROMIC OROFACIAL CLEFT IN COMBINED CLEFT CLINIC UNIVERSITI MALAYA FROM 2000-2020

ABSTRACT

Introduction: Syndromic orofacial cleft is not a typical encounter and poses significant challenges to clinicians in regard to the patient's management due to underlying comorbidities. **Objectives:** This study aims to describe the prevalence of syndromes and congenital anomalies associated with orofacial cleft, to determine the types of cleft associated with syndromic and nonsyndromic orofacial cleft patients, to compare the treatment timeline of primary cleft lip and palate repair in syndromic and nonsyndromic orofacial cleft patients with standard guidelines and to determine the complications encountered in managing syndromic orofacial cleft patients. **Materials and methods:** This is a 20-year retrospective study involving 676 patients. The patient's clinical data was extracted. Descriptive statistical analysis was conducted to determine the prevalence of different variables. Chi-square and Fisher's exact test were performed to determine the significant association in the age of primary lip and palate repair of syndromic and nonsyndromic patients. All data were analysed using SPSS version 29. **Results:** The total number of syndromic patients was 11.4% and nonsyndromic was 88.6%. Unilateral cleft lip and palate (39.4%) is the most common subtype in nonsyndromic orofacial cleft patients. For syndromic orofacial cleft patients, cleft palate (67.5%) is highly prevalent. Pierre Robin sequence (37.66%) is the most common syndrome associated with orofacial cleft. The most common congenital anomaly in orofacial cleft patients is the circulatory system (22.3%). In syndromic patients, face, mouth or teeth anomalies (22.2%) are highly observed. Syndromic orofacial cleft patients have a significant delay in primary lip repair. Most complications of primary repair in syndromic orofacial cleft patients are related to airway issues, pyrexia and bronchopneumonia. **Conclusion:** The prevalence of

syndromes and congenital anomalies in orofacial cleft patients attending Combined Cleft Clinic, Faculty of Dentistry, Universiti Malaya is comparable to previous studies. Routine screening for congenital anomalies is recommended, especially in syndromic orofacial cleft patients. The data on differences in treatment timing for primary repair in syndromic patients can be used as a guide in consultations with parents.

Keywords: Syndromic, orofacial cleft, congenital anomalies

KAJI SELIDIK UMUM SINDROM KLEF OROFASIAL DI KLINIK KLEF GABUNGAN UNIVERSITI MALAYA DARI 2000- 2020

ABSTRAK

Pengenalan: Sindrom klef orofasial bukanlah satu pertemuan biasa dan menimbulkan cabaran yang ketara kepada pengamal perubatan berkaitan pengurusan pesakit disebabkan komorbiditi yang mendasari. **Objektif:** Kajian ini bertujuan untuk menerangkan kelaziman sindrom dan anomali kongenital yang berkaitan dengan klef orofasial, untuk menentukan jenis klef berkait dengan pesakit sindrom klef orofasial dan bukan sindrom, untuk membandingkan garis masa rawatan pembaikan klef bibir dan lelangit di antara pesakit sindromik dan bukan sindrom dan untuk menentukan komplikasi yang dihadapi dalam menguruskan pesakit sindrom kleft orofasial. **Bahan dan kaedah:** Ini adalah kajian retrospektif 20 tahun yang melibatkan 676 pesakit. Data klinikal pesakit telah diekstrak. Analisis statistik deskriptif telah dijalankan untuk menentukan prevalens pembolehubah yang berbeza. Ujian khi kuasa dua dan ujian tepat Fisher dilakukan untuk menentukan perkaitan yang signifikan dalam umur pembaikan bibir dan lelangit primer pesakit sindrom dan bukan sindrom. Semua data dianalisis menggunakan SPSS versi 29. **Keputusan:** Jumlah pesakit sindromik ialah 11.4% dan bukan sindromik ialah 88.6%. Sumbing bibir dan lelangit unilateral (39.4%), adalah subjenis yang paling biasa dalam pesakit sumbing orofasial bukan sindrom. Bagi pesakit sumbing orofasial sindrom, lelangit sumbing (67.5%) adalah sangat lazim. Urutan Pierre Robin (37.66%) adalah sindrom yang paling biasa dikaitkan dengan klef orofasial. Anomali kongenital yang paling biasa dalam pesakit celah orofasial ialah sistem kardiovacular (22.3%). Dalam pesakit sindrom, anomali muka, mulut atau gigi (22.2%) sangat ketara. Pesakit klef orofasial sindrom mempunyai kelewatan yang ketara dalam pembaikan primer bibir.

Kebanyakan komplikasi pembaikan primer dalam pesakit klef orofasial sindrom berkaitan dengan masalah saluran pernafasan, demam dan bronkopneumonia.

Kesimpulan: Prevalens sindrom dan anomali kongenital pada pesakit sumbing orofasial yang menghadiri Klinik Sumbing Gabungan, Fakulti Pergigian, Universiti Malaya adalah setanding dengan kajian terdahulu yang dijalankan. Pemeriksaan rutin untuk anomali kongenital disyorkan terutamanya pada pesakit klef orofasial sindromik. Data dalam perbezaan masa rawatan untuk pembaikan primer dalam pesakit sindrom boleh digunakan sebagai panduan dalam perundingan dengan ibu bapa.

Kata kunci: Sindrom, klef orofasial, anomali kongenital

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LIST OF SYMBOLS AND ABBREVIATIONS

CLP	:	Cleft lip and palate
CL/P	:	Cleft lip and/or cleft palate
CL	:	Cleft lip
CP	:	Cleft palate
CPO	:	Isolated cleft palate
NCC	:	Neural crest cells
ENT	:	Ear, nose and throat
PRS	:	Pierre Robin Sequence
ICD-11	:	International Classification of Diseases version 11
PICU	:	Paediatric Intensive Care Unit
GIT	:	Gastrointestinal tract
CNS	:	Central nervous system

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CHAPTER 1: INTRODUCTION

Orofacial clefts are one of the most prevalent head and neck congenital deformities and may be associated with other syndromes or congenital anomalies. The orofacial cleft can be classified by anatomical location, such as cleft lip, cleft palate, unilateral cleft lip and palate and bilateral cleft lip and palate. It can also be divided into nonsyndromic or syndromic forms. Multiple classifications of the orofacial cleft are recommended in the literature, mainly based on anatomical systems useful for surgeons and embryology-based systems for genetic counselling and research (Mooney, 2008).

"Syndrome" is a distinct pattern of abnormalities associated with a specific cause. While "association" is a non-random, statistically significant relationship of multiple anomalies for which no particular aetiology can be detected and "sequence" is a pattern of various anomalies caused by an aberration that leads to a chain reaction of secondary effects. It is also crucial to acknowledge that these aren't mutually exclusive. A congenital anomaly, also known as a birth defect, congenital malformation, or congenital aberration, is an abnormal structural or functional birth defect. A structural defect is an abnormality in the organs and skeleton of the body. In contrast, a functional defect is a malfunction in the operation of a body system, such as metabolic disorders, brain and nervous system disorders, degenerative diseases, immune disorders, and sensory disorders (Gomella et al., 2020). Syndromic orofacial cleft refers to the presence of orofacial cleft as a primary feature and additional physical or cognitive abnormalities caused by the mutation of a single genetic locus, chromosomal abnormalities or teratogens(Leslie & Marazita, 2013).

A systematic review of global orofacial cleft prevalence was conducted in 2015. The result showed 45,193 patients with orofacial cleft in a study population of 30,665,615 live births. According to continents, the orofacial cleft birth prevalence from Asia, North America, Europe, Oceania, South America, and Africa were 1.57, 1.56, 1.55, 1.33, 0.99,

and 0.57 per 1,000 live births, respectively. The American Indians had the highest prevalence rates of 2.62 per 1,000 live births, followed by the Japanese, the Chinese, and the Whites of 1.73, 1.56, and 1.55 per 1,000 live births, respectively. The Blacks had the lowest rate of 0.58 per 1,000 live births (Panamonta et al., 2015). A study in the United States reported the prevalence of cleft lip and palate associated with a known syndrome was only 8%, and 17% of cases had other congenital malformations (Watkins et al., 2014). A population-based retrospective study in Italy revealed that 29.8% of 739 patients were syndromic or had multi-malformed anomalies (Impellizzeri et al., 2019).

Research of cleft lip and palate in neonates born in the Maternity Hospital Kuala Lumpur conducted from 1986 to 1987 revealed 52,379 babies delivered. Sixty-four were born with cleft lip and/or palates. The rate of occurrence of cleft was 1.24 per 10 live births or 1.20 per 10 deliveries. The most common type was unilateral cleft of the primary and secondary palate (Boo & Arshad, 1990). Another Malaysian multicentre retrospective epidemiology study to capture the demographic of oral cleft characterisation was done from 2003 to 2007. The results of this study show that 57% of females and 43% of males were affected by oral cleft. Out of the total patients, 77.8% were CLP, 13.5% were cleft palate (CP), and 8.7% were cleft lip (CL) patients. Moreover, 57.2% of patients had unilateral cleft, 32.7% were left-sided, and 24.5% were right-sided. 42.8% of patients had bilateral oral cleft (Shah et al., 2015). However, limited study was done to provide epidemiological data, mainly in syndromic orofacial patients in Asia, particularly in the Malaysian population.

1.1 Aim

To describe the management of syndromic orofacial cleft patients seen in the Combined Cleft Clinic, Department of Oral and Maxillofacial Clinical Sciences, Faculty of Dentistry, Universiti Malaya from year 2000 to year 2020.

1.2 Objectives

i) To determine the prevalence of syndromes and congenital anomalies associated with orofacial cleft.

ii) To determine the types of cleft associated with syndromic and nonsyndromic orofacial cleft patients.

iii) To compare the treatment timeline of primary cleft lip and palate repair in syndromic and nonsyndromic orofacial cleft patients with standard guidelines.

iv) To determine the complications encountered in managing syndromic orofacial cleft patients.

1.3 Null hypothesis

i) There is no difference in the management of syndromic orofacial cleft patients compared to nonsyndromic patients seen in the Combined Cleft Clinic, Department of Oral and Maxillofacial Clinical Sciences, Faculty of Dentistry, Universiti Malaya

CHAPTER 2: LITERATURE REVIEW

2.1 Embryology of Orofacial Cleft

Orofacial development is a multistep process that involves a series of well-coordinated events, including cellular proliferation, migration, apoptosis, differentiation, and tissue fusion. Between the fourth and twelfth weeks of gestation, the lips, palate, nostrils, and mouth are formed during facial development. In embryonic development, cell migration, the fusion of facial processes, and tissue differentiation are the three significant events. In the fourth week of gestation, specialised neural crest cells (NCC) migrate to the frontonasal and visceral arch regions and develop into five facial structures or primordia. The maxillo-mandibular complex is composed of these primordia: the paired mandibular prominences, the maxillary prominences, and the frontonasal prominence. Normal lip formation takes place between the fourth and eighth weeks of pregnancy. The lateral portions of the upper lip are formed when the maxillary prominences fuse with the lateral nasal prominence as they grow medially. Additionally, the maxillary prominences give rise to the cheekbones, whereas the lateral nasal prominences give rise to the alae of the nose. Around week 5 of gestation, the maxillary prominences continue to grow medially and fuse with the medial nasal prominence on either side, bringing the nostrils closer together. The intermaxillary segment formed due to the fusion of the medial nasal prominences. This results in the development of the philtrum and the middle one-third of the upper lip, the primary palate, the central nostril, and the nasal septum. Failure of this procedure will result in a cleft lip. Palate formation occurs between the fifth and twelfth weeks of gestation. The most crucial stage occurs between the sixth and ninth weeks and the primary palate forms in week seven. The secondary palate originates from the paired lateral palatine processes (palatal shelves), which develop from the medial aspect of the maxillary prominences. Elevation and fusion of the palatal shelves are made possible by increased muscular development and tongue

flattening. At the 12th week of gestation, facial development is complete (Bernheim et al., 2006; Burdi, 2006). The anterior extent of the secondary palate is marked by the incisive foramen. Due to the sequential nature of normal development, a cleft lip may or may not be associated with a cleft palate. Similarly, isolated cleft palates can occur without cleft lips (Meyers, 1993).

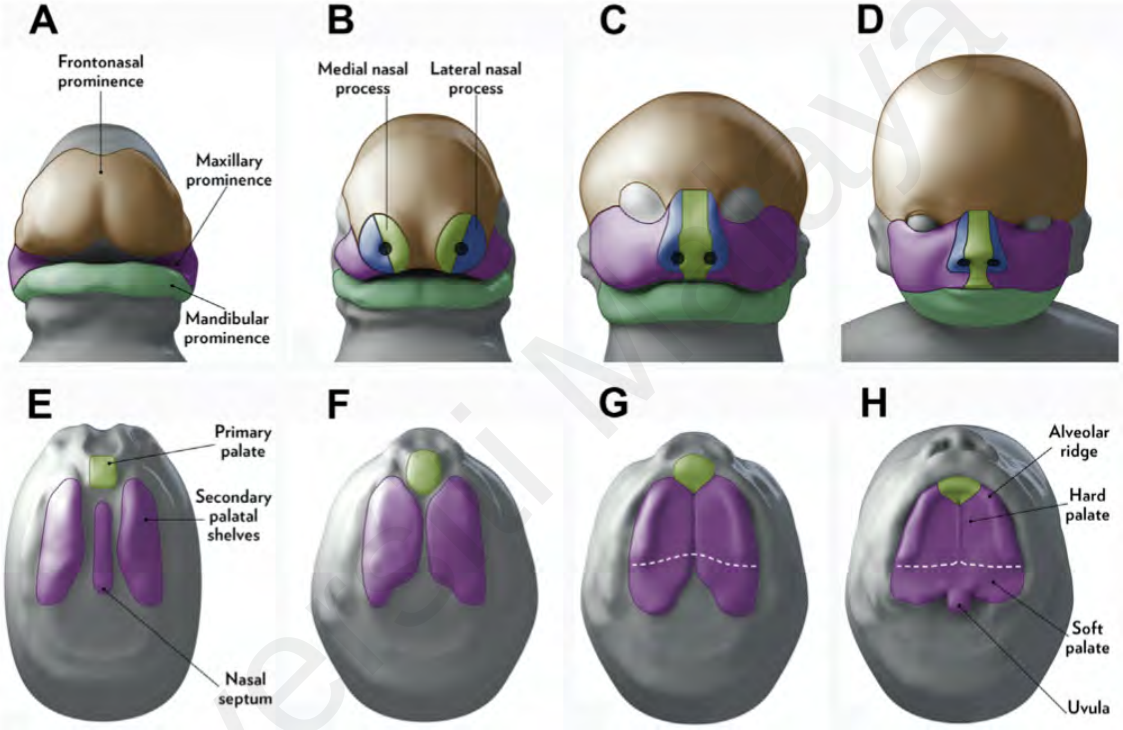

Figure 1: (A-D) Upper lip development sequence. (E-H) Soft and hard palate development. (Note: Adapted from Worley, M. L., Patel, K. G., & Kilpatrick, L. A. (2018). Cleft Lip and Palate. *Clin Perinatol*, *45*(4), 661-678. Illustration by Emma Vought.)

2.2 Aetiology of Orofacial Cleft

It was recognised that genetic predisposition is an essential aspect of cleft lip and palate. According to investigations of monozygotic twins, genetic susceptibility accounts for 40–60% of orofacial clefting (Grosen et al., 2011). The production of transcription

factors that can be translated into structural, regulatory, or enzymatic proteins controls early embryonic development genes (Sperber, 2002). These growth factors and morphogens target specific populations of embryonic cells and their signal transduction pathways, leading to increasing differentiation, migration, shape changes (morphogenetic movements), and programmed cell death (apoptosis) of these cells. Inductive biochemical and biomechanical interactions between these cell groups may cause specific cell populations to differentiate independently, even without the inducing tissue (Johnston & Bronsky, 1995).

It has been established that the epithelial-to-mesenchymal transition (EMT) is the key mechanism that drives palate and shelf fusion (Iordanskaia & Nawshad, 2011), cell migration, and apoptosis (Vaziri Sani et al., 2005). A vast array of signalling molecules, including sonic hedgehog signalling molecules (SHH), transforming growth factors (TGFs), fibroblast growth factors (FGFs), and bone morphogenetic proteins (BMPs), as well as various developmental transcription factors, including msh homeobox (MSX) and the T-Box (TBX) gene families, have been identified as mediators of cellular growth, proliferation, patterning, migration, apoptosis, and EMT interactions (Francis-West et al., 1998; Minoux & Rijli, 2010; Rahimov et al., 2012). Therefore, mutations in these genes could significantly affect orofacial development (Cordero et al., 2011). The key genes associated with craniofacial morphogenesis are as follows:

Table 2.1: Key Genes associated with Craniofacial Morphogenesis

Cellular function	**Molecules**
Cell adhesion molecules	Cnx43, E-cad, Pvrl1
Extracellular matrix	Col2A1, Col11A1, Col11A2, FN1, MMP2, MMP3, MMP9, MMP13, TIMP1-3
Growth factors and receptors	EGF, EGFR, FGF1, FGF2, FGF8, FGFR1, FGFR2, TGFα, TGFβ1-3
Polarising signals	Bmp2, Bmp4, Bmp7, SHH, Smad2-4, WNT5a
Transcription factors	Ap2α, Dlx1–6, Gli2-3, Hoxa2, IRF6, Lhx8, Msx1, Pax9, Pitx1, Pitx2, Prx1, Tbx1, Tbx22

Note: Adapted from Nasreddine, G., El Hajj, J., & Ghassibe-Sabbagh, M. (2021). Orofacial clefts embryology, classification, epidemiology, and genetics. *Mutation Research/Reviews in Mutation Research*, *787*, 108373.

The aetiologies of syndromic orofacial cleft include association with a specific Mendelian disorder and a single gene mutation, chromosomal structural abnormalities, syndromes resulting from known teratogens or idiopathic aetiologies that are unclear and, therefore, unidentified at this time (Ashouri et al., 2021). However, identifying the underlying mechanisms presents additional difficulties. Various syndromic diseases that can include orofacial clefts are heterogeneous in both genotype and phenotype, and the presentation of a cleft in conjunction with other defining characteristics is frequently penetrance-dependent. For many syndromic conditions in which clefts are uncommon, it may be challenging to determine the underlying aetiologies associated with an orofacial cleft phenotype. Numerous disease-causing genes and factors are present, and the role of specific genes in cleft-associated cases may not be as thoroughly described, mainly if clefts are a minor symptom and not the primary focus of research on a particular condition. In addition, many syndromes are caused by deletions that disrupt multiple genes, complicating the link between specific loci and lip or palate fusion. When a case study of a smaller group or individual patient is available alongside mutation data, it is

frequently possible to attribute the orofacial cleft to a specific gene or locus mutation (Reynolds et al., 2020).

Nonsyndromic clefts are typically categorised as polygenic and multifactorial disorders. The threshold model describes the manifestation of a multifactorial disease when environmental and genetic factors interact and exceed a predetermined threshold. Decades of research have been devoted to identifying genetic and environmental risk factors for orofacial cleft. An extensive review described several known genes that play a role in the development of nonsyndromic cleft lip and palate in the Asian population (Ashouri et al., 2021). The genes susceptible for nonsyndromic orofacial cleft formation include:

-IRF6 (interferon regulatory factor 6) is located on 1q32.2 and performs a role in the development of embryonic tissues. It controls bone differentiation, mineralisation during embryonic and foetal development, and many other actions. In craniofacial tissues, IRF6 is expressed in osteocytes and hypertrophic chondrocytes (Xia et al., 2017).

- MTHFR (methylenetetrahydrofolate reductase) is a significant enzyme of folic acid metabolism located on 1q36. Multiple studies have demonstrated the role of MTHFR polymorphism in the folate pathway. CLP is associated with the homozygosity pattern for rs1801133 polymorphism in MTHFR (de Aguiar et al., 2015).

- BMP4 (bone morphogenetic protein 4) resides on 14q22. 2 and is an important regulatory molecule that plays a crucial function in bone induction, tooth formation, and facial development. BMP4 modifies growth factor molecules with vital roles in embryonic development. Dysfunction of the BMP4 caused cranial and facial malformations to develop, including CLP (Saket et al., 2016).

- SHTN1 (shootin 1) resides on a 10q25. It is a protein-coding gene expressed in the proximal maxilla that contributes to axon formation, growth, and morphogenesis, plays a role in developing craniofacial structures, and is involved in neural polarisation. SHTN1 is also essential for cell migration and nervous system development (Li et al., 2018).

- NOG (Noggin) resides on chromosome 17q22. NOG is expressed at multiple sites, including developing bones; it modulates BMP signalling and is necessary for palatal epithelial integrity and normal palate growth (He et al., 2010).

- The location of TPM1 (tropomyosin alpha-1) is 15q22. It is a tropomyosin (Tm) family member that regulates calcium during muscle contraction in smooth muscle and the cytoskeleton of non-muscle cells and protects the ubiquitous group of actin-binding proteins involved in muscle contraction and cytoskeletal organisation (Qian et al., 2016).

- FGF1 (fibroblast growth factor 1) resides on chromosome 5q31. Multiple congenital diseases of the human musculoskeletal system are influenced by mutations in this gene (Rafiqdoost et al., 2014).

- GLI2 (GLI family zinc finger 2) resides on chromosome 2q14. In vertebrates, GLI2 is a specific transcription factor that regulates transcription in the hedgehog (Hh) pathway and is involved in intracellular signal transmission (Meng et al., 2019).

- TGFA (transforming growth factor-alpha) resides on chromosome 2p13. 3. It is one of the epidermal growth factor types associated with some cases of cleft lip/palate (Saket et al., 2016).

There were a few environmental causes of nonsyndromic orofacial cleft. Nutritional deficiencies in vitamins B6, B12, and folate are critical for orofacial cleft formation. During pregnancy, infections can induce congenital disabilities. It is essential to avoid

exposure to viruses like rubella and cytomegalovirus. Teratogen exposure in pregnant women, like corticosteroids, retinoids, phenytoin, epiroic acid, thalidomide, certain drugs, including antiepileptic drugs, and common exposures to alcohol or dioxin, has been linked to CP. Orofacial clefts are associated with maternal smoking, particularly in the first trimester of pregnancy. The most significant prevalence of cleft is observed in pregnant women who smoke and drink heavily (Moreira et al., 2016).

2.3 Syndromes associated with Orofacial Cleft

Over 500 Mendelian syndromes with OFCs are listed in the Online Mendelian Inheritance in Man (OMIM) database (Shkoukani et al., 2013). Van der Woude syndrome (VWS) is the most prevalent type of syndromic cleft. A significant proportion of cases are caused by IRF6 mutations, which are also associated with the dominant popliteal pterygium syndrome (PPS). This condition usually involves CL/P and affects the skin and genitals (Kondo et al., 2002). It is transmitted as an autosomal dominant trait, and the lower lip pit is the defining characteristic. These pits are bilaterally located in the lower lip at the junction of dry and moist vermilion and are oval or transverse in shape. The pits traverse the orbicularis muscle and terminate in a blind cavity on the buccal side, where they communicate with minor salivary glands. Associated characteristics include hypodontia, absence of maxillary or mandibular second premolar teeth, absence of maxillary lateral incisor, and ankyloglossia. Other uncommon extraoral manifestations include accessory nipples, congenital cardiac defects, Hirschsprung disease, and popliteal web (Martelli-Junior et al., 2007).

The Pierre-Robin sequence (PRS) is a group of frequently observed craniofacial phenotypes, including glossoptosis, cleft palate, micrognathia, and upper airway obstruction. Palate defects appear to be secondary effects resulting from altered tongue and mandible positioning as opposed to intrinsic defects within the palatal shelves. The

dominant paradigm postulates that mandibular hypoplasia results in a high, retrotransposed tongue obstructing palatal shelves elevation and the upper airway. Alternately, intrauterine compression of the mandible may limit its growth and modify the development of the tongue, similarly obstructing the palate and airway. A third theory proposes that delayed neuromuscular development diminishes the tongue's capacity to stimulate mandible and palate growth, resulting in the observed phenotypes (Giudice et al., 2018). This sequence is frequently recognised as part of a broader syndrome, though this is not always true. Mutations in or near the SRY-related HMG box 9 (SOX9) locus have been linked to isolated PRS (Benko et al., 2009; Jakobsen et al., 2007). Stickler syndrome and the analogous Marshall syndrome are frequently associated with PRS and can be caused by mutations in multiple collagen genes (Guo et al., 2017).

Craniosynostosis occurs due to the untimely fusion of cranial bones and is often accompanied by oral clefts in syndromic cases. These syndromes have been linked to altered Fgf signalling, specifically FGFR2 variants. Both Apert and Crouzon syndromes are characterised by craniosynostosis and can include cleft palate, and both are associated with FGFR2 mutations (Reardon et al., 1994; Slaney et al., 1996; Wilkie et al., 1995).

Robinow syndrome is a form of skeletal dysplasia that affects limb and genital development; frequent craniofacial characteristics include CL/P or CPO. It results from mutations in multiple gene signalling (Reynolds et al., 2020).

22q11.2 deletion syndrome, or velo-cardio-facial syndrome, is a spectrum of disorders associated with a chromosome 22 genomic deletion. It influences the development of the neural crest, resulting in a distinct craniofacial phenotype (Reynolds et al., 2020). Microcephaly, malar flattening, mandibular retrusion, overfolded or squared-off helices, prominent nasal root, bulbous nasal tip, hooded eyelids, and hypertelorism are the craniofacial characteristics. Congenital heart disease (including

conotruncal malformations such as tetralogy of Fallot, interrupted aortic arch, ventricular septal defects, or truncus arteriosus) and palatal abnormalities (velopharyngeal incompetence, submucosal cleft palate, and cleft palate) represent the remaining spectrum of malformations (Gomella et al., 2020).

Median facial dysplasia is a unique, distinct, definable group of patients characterised by midline facial deficiencies in the presence of a unilateral or bilateral cleft lip with or without cleft palate(Noordhoff et al., 1993). The midline hypoplasia may extend into the midline structure of the brain, like the corpus callosum. If the head circumference is <90% of normal, these patients may have associated anomalies of the brain, especially the frontal corpus callosum (Venkatesh, 2009).

CHARGE syndrome is another syndrome associated with orofacial cleft. The acronym "CHARGE" was introduced in 1981, and the phenotype includes colobomas, heart defects, choanal atresia, delayed development, genital hypoplasia, auditory anomalies and deafness (Pagon et al., 1981). This syndrome is caused by chromodomain helicase DNA 7 (CHD7) mutations (Vissers et al., 2004). Since the multiple congenital anomalies of CHARGE are pathogenetically linked to a single locus, the disorder is currently classified as an autosomal dominant syndrome (Graham, 2001; Lubinsky, 1994; Verloes, 2005).

Orofacial deformity is also associated with amniotic band sequence. It was caused by the effects of an early amnion rupture, with the principal event being the entanglement of body parts in bands or strands of amnion. The biomechanical forces that result in disruptions, deformations, and malformations. Viscera that are typically outside the foetus during early embryonic development may be prevented from returning, resulting in an omphalocele, ectopia cordis, thoracoschisis, or abdominoschisis. Extremity anomalies include congenital amputations, constrictions, and distal enlargements.

Microcephaly, encephaloceles, and facial clefts are examples of craniofacial anomalies (Gomella et al., 2020).

2.4 Congenital Anomalies Associated with Orofacial Cleft

Single-system or multiple-system malformations are the two main classifications for congenital anomalies. The first type affects only one organ or body part, whereas the second type affects multiple organ systems or body parts (al-Gazali et al., 1995; Sawardekar, 2005; Walden et al., 2007). The majority of structural abnormalities occur during the critical period of foetal development in the first trimester. Heart anomalies, neural tube defects, and clubfoot are examples of structural defects. Major anomalies necessitate medical and surgical treatment, including congenital heart defects, anencephaly, gastroschisis, cleft lip/palate, and meningomyelocele (Gomella et al., 2020). It could significantly impair normal body functions or even reduce life expectancy if not treated. Minor anomalies do not result in disability or significant physical or functional effects and can be considered normal variants (al-Gazali et al., 1995; Anyanwu et al., 2015; Kingston, 2002). Single palmar creases, epicanthal creases, and fifth digit clinodactyly are examples of minor anomalies. 75% of newborns with significant congenital anomalies have a single anomaly, while 25% have multiple anomalies (Gomella et al., 2020).

In the reported literature, the organ system or region most frequently affected by associated anomalies in CL/P patients varies. In the majority of studies, anomalies were reported to be more prevalent in the extremities, cardiovascular and central nervous systems, and facial region; however, the exact prevalence of each system/area varied (Abyholm, 1978a, 1978b; Calzolari, 2007; Lilius, 1992; Milerad et al., 1997; Rawashdeh & Jawdat Abu-Hawas, 2008; Shafi et al., 2003; Shprintzen et al., 1985; Stoll et al., 2000). Previous studies of associated anomalies with orofacial cleft showed facial anomalies

were most frequently detected, followed by the ocular system, central nervous system, lower and upper extremities, and cardiovascular (Sekhon et al., 2011). According to another study, congenital cardiac anomalies are the most common anomaly associated with orofacial cleft. Other congenital anomalies included micrognathia unique to cleft palate, congenital hydrocephalus, talipes equinovarus, ectopic kidney, brachycephaly, and syndactyly (Hadadi et al., 2017). Holoprosencephaly is another form of congenital anomaly of the nervous system. It is characterised by the failure of the forebrain to form two hemispheres and is frequently associated with abnormalities in the craniofacial structures of the midface. Holoprosencephaly with CL/P is associated with mutations in the genes that code for the transcription factor Sine oculis homeobox 3 (SIX3) and the Nodal/ TGF-B modulator transforming growth-interacting factor (TGIF1) (Aguilella et al., 2003; Gripp et al., 2000; Lacbawan et al., 2009; Wallis et al., 1999).

2.5 Comprehensive Treatment of Orofacial Cleft

The American Cleft Palate-Craniofacial Association stresses the significance of multidisciplinary treatment for orofacial cleft patients within the first few days of their lives ("Parameters For Evaluation and Treatment of Patients With Cleft Lip/Palate or Other Craniofacial Differences," 2018). In view of the prevalence of associated abnormalities, a prompt evaluation of dysmorphology is necessary. A comprehensive genetic evaluation should be considered if additional abnormalities are detected. Once a neonate has been referred to a craniofacial team, a coordinator can also assist families in planning their care after discharge. Patients with CLP often require the care of multiple medical specialities (Table 2.2) and should be followed in a multidisciplinary clinic until early adulthood (Worley et al., 2018).

Table 2.2: Multidisciplinary Cleft Care

Age	Medical treatments	Surgery
Prenatal to birth	• Genetic counselling • Speech-language pathology consultation for feeding	-
0 – 5 months old	• Speech-language pathology consultation for feeding and growth • Monitor hearing • Nasoalveolar moulding (if indicated)	• Cleft lip repair • Ear tube (if chronic otitis media)
9-12 months old	-	• Palatoplasty • Ear tube if chronic otitis media
1-4 years old	• Introduction to Paediatric dentist • Assess language development	-
4-6 years old	• Assess for velopharyngeal dysfunction	• Corrective speech surgery • Lip revision, if needed • Minor nasal surgery, if needed
6-12 years old	• Orthodontics • Assess school or psychosocial adjestment	• Alveolar bone grafting
12- 21 years old	• Orthodontics	• Orthognathic surgery • Definitive rhinoplasty

Note: Adapted from Worley, M. L., Patel, K. G., & Kilpatrick, L. A. (2018). Cleft Lip and Palate. *Clin Perinatol*, *45*(4), 661-678.

The multidisciplinary team includes dental, medical, and allied health sciences specialists. The dental team comprises a paediatric dentist, a prosthodontist, an oral and maxillofacial surgeon, and an orthodontist. The medical team includes a plastic surgeon, paediatrician, psychiatrist, medical geneticist, and ENT surgeon or otolaryngologist. The speech therapist, audiologist, nursing staff, and social worker are specialists in allied health sciences (Freitas et al., 2012). Another author categorised the treatment sequence for orofacial deformity based on dentition stages (Farronato et al., 2014; Nahai et al., 2005) :

- Stage I: Maxillary Orthopedic Stage (Birth to 18 months)
- Stage II: Primary Dentition Stage (18 months to 5 years of age)
- Stage III: Late Primary or Mixed Dentition Stage (6 to 10 or 11 years of age)
- Stage IV: Permanent Dentition Stage (12 to 18 years of age)

During the neonatal period, lip taping and nasoalveolar moulding (NAM) are frequently used presurgical interventions to reduce the severity of a cleft deformity. Reduced cleft width, enhanced nasal symmetry, and improved psychological outcomes for carers are suggested as advantages of these interventions (Pool & Farnworth, 1994; Sabarinath et al., 2010; Sischo et al., 2016; van der Heijden et al., 2013). However, controversy persists regarding the efficacy of specific techniques, and clinical practice patterns vary widely (Rodman & Tatum, 2016; Sitzman et al., 2008). Routinely, neonates with complete CL had their lips taped. Within one week of birth, the tape is applied across the fissure while the lip is squeezed together. Prior to discharge, families are instructed on how to use the tape daily and are scheduled to return to the cleft surgeon's clinic for follow-up care. Skin irritation is the most prevalent complication of lip taping. A dressing can be applied before taping to safeguard the skin (Worley et al., 2018). The optimal timing of surgical repair is determined by surgeon preference, anaesthetic risks, comorbid

congenital anomalies, and perceived psychological impact on the family (Vyas et al., 2020). The majority of surgeons restore cleft lips between 10 and 12 weeks of age. The rule of 10 still holds. Wilhelmsen and Musgrave recommended that cleft lip correction be performed when the patient reaches the following; weight over 10 lbs, 10 g/dL haemoglobin, and 10,000 mm3 white blood cell count (Wilhelmsen & Musgrave, 1966).

Palatoplasty is performed between 12 and 18 months of age. Its principal function is to promote normal speech patterns. A cleft palate can be surgically closed in either one or two stages. The hard palate is repaired in a single stage between 12 and 18 months using the mucoperiosteal flap technique. In a two-stage procedure, the soft palate is repaired before 18 months, and the hard palate is obliterated until the second stage. Within four to five years, the hard palate is repaired during the second phase of treatment. (Subramanyam, 2020).

The primary dentition stage focuses on establishing oral health between 18 months and five years old. To prevent dental caries, effective oral hygiene practices are utilised. During this stage, abnormal eruption of primary maxillary anteriors around the cleft defect is expected, so recall and examinations are undertaken every three to four months (Rao, 2008). Orthodontists perform a crucial role during the stage of mixed dentition, which occurs between the ages of 6 and 11. Either the NiTi arch Expander or the Quad Helix can be utilised to expand an arch. Maxillary Protraction is performed with a reverse-drawing head mechanism. Before the eruption of the canine, a secondary bone graft is placed; when the canine erupts through the graft, stability of the maxillary segment is achieved (Hodgkinson et al., 2005). The final correction is made during permanent dentition between the ages of 12 and 18. The misaligned teeth are corrected orthodontically; the canine is exposed and realigned if it has not yet erupted. Rehabilitation is conducted using a fixed bridge or cast partial denture. If indicated, lip

revision surgery, orthognathic surgery, and rhinoplasty are performed following orthodontic treatment (Subramanyam, 2020).

2.6 Perioperative Complications in Primary Cleft Lip and Palate Surgery

Early cleft lip and palate closure can result in many known and life-threatening complications, including mortality, bleeding, and upper airway obstruction (Liao et al., 2010; Lohmander et al., 2009). In previous years, these complications were dreaded and occasionally unexplained. The "five-ten" rule (10-g haemoglobin, the cells white blood cell count less than 10,000 mm3, no history of the upper respiratory tract in the past 10 days, 10 weeks of age, and 10 pounds of body weight) strictly adhered to, which increased surgical safety and decreased the incidence of complications was now observed (Losee et al., 2008). With the advancement of anaesthesia and resuscitation techniques, the age of closure can be reliably reduced to the early postnatal period in some cases. Overall, a low incidence has been obtained, which can be attributed to the collaboration of a team of highly specialised professionals (Losken et al., 2011).

Early studies have found that the significant complications associated with primary lip repair are postoperative haemorrhage, repair failure, and pneumonia. Minor complications include diarrhoea, otitis media, partial separation of the suture line, and mild upper respiratory infection (Wilhelmsen & Musgrave, 1966). Later investigations identified complications related to bleeding, difficulty feeding, wound dehiscence, wound infection, pneumonia, respiratory compromise, and respiratory arrest (Eaton et al., 1994; Lees & Pigott, 1992; Wood, 1994). Unilateral CL repair surgical complications include deficient vermilion or a whistle deformity, under-rotation of the high point on the cleft side, muscular dehiscence, and nasal asymmetry. Typically, secondary lip surgery can be planned at approximately five years of age or older. Short-term complications of primary palatal repair include haemorrhage, infection, tongue oedema, and respiratory

impairment. The need for postoperative hospitalisation and nutrition plan (i.e., bottle versus open-flow cup) should also be discussed with the parents prior to surgery. Palatoplasty aims to restore an intact levator palatini and elongate the palatine arch; ideally, the surgery should have a low incidence of palatal fistula, velopharyngeal dysfunction, and maxillary growth disturbance (Worley et al., 2018). Palatoplasty is associated with complications such as palatal fistula, obstructive sleep apnea, and velopharyngeal dysfunction. Formation of a fistula is associated with nasal regurgitation of oral intake and hypernasality. It results in ineffective speech, fluid regurgitation, and facial grimacing. It is treatable with a pharyngoplasty utilising a palatopharyngeal flap (Nam, 2018). Patients with clefting have a higher incidence of obstructive sleep apnoea; therefore, screening for symptoms of sleep-disordered breathing should be performed routinely in this patient population (Muntz et al., 2008). Given their high-risk status, a polysomnogram is recommended before additional surgical intervention (Marcus et al., 2012).

Another study investigated the side effects of primary cleft lip and palate surgery. The author divided complications into those that occurred within two weeks and those that lasted longer than two weeks. The overall complication rate was 16.8%. Asphyxia, fever, oedema of the respiratory tract, upper respiratory tract infection, bronchiolitis, pneumonia, diarrhoea and vomiting, bleeding, odontoptosis, erosion of the corner of the mouth, drowsiness, incision dehiscence, wound infection, palatal dehiscence/fistula, nasal floor breakdown, conjunctivitis, and mortality were among the early complications. Secondary lip/nasal deformity, dehiscence of the lip, palatal fistula/decencies, hearing problem/otitis media, poor ventilation/snoring, velopharyngeal incompetence, and voice disorder were the long-term complications (Zhang et al., 2014). An additional study of primary lip and palate repair complications in adults and infants has been conducted. The authors classified complications as major (wound breakdown, postoperative

haemorrhage), minor (partial wound breakdown, vermillion notching, hypertrophic scar), and general (diarrhoea, malaria, upper respiratory tract infection, lower respiratory tract infection). Children have a high complication rate, which consists primarily of minor and general complications (complications owing to cross-infection). However, adult patients exhibited a higher incidence of serious complications. Upper respiratory tract infection was the most prevalent general complication (Adesina et al., 2016). However, due to the small sample size from a particular centre, the results of this study do not reflect the actual population.

CHAPTER 3: MATERIALS AND METHODS

3.1 Study Design

This is a cross-sectional study utilizing retrospective data of the patients seen in the Combined Cleft Clinic, Faculty of Dentistry, Universiti Malaya, from the year 2000 to the year 2020. The study sample consisted of records of every patient registered in the Combined Cleft Clinic, Faculty of Dentistry, Universiti Malaya, from year 2000 to year 2020.

The inclusion criteria for the study were as follows:

i. All orofacial cleft cases registered at the Combined Cleft Clinic, Faculty of Dentistry, Universiti Malaya include pediatric and adult patients.

The exclusion criteria were as follows:

i. Incomplete case records such as no definitive diagnoses of types of cleft and types of syndromes, no surgical records of primary lip and palate repair.

All clinical data was extracted from the patient's clinical records.

3.2 Data collection

A total of 851 patients were registered in the Combined Cleft Clinic, Faculty of Dentistry, Universiti Malaya, from 2000 to 2020. After screening through the records, 175 patients were excluded due to incomplete data. Patients' demographic data, diagnoses, syndromes, congenital anomalies, age of primary lip and palate repair conducted and any complications of primary lip and palate repair were recorded.

The following baseline demographic data was collected:

i. Gender: Male, and female

ii. Race: Malay, Chinese, Indian, Bumiputera (Sabah/Sarawak), and others

The clinical data of the patients were collected including:

i. Types of cleft

It was classified based on the following anatomical phenotypes:

- Bilateral cleft lip and palate
- Unilateral cleft lip and palate
- Cleft lip
- Cleft lip and alveolus
- Submucous cleft
- Facial cleft

ii. Types of syndrome

iii. The associated congenital anomalies

It was grouped by system, following the World Health Organization (WHO) Eleventh Revision of the International Classification of Diseases (ICD-11). The descriptive details of associated anomalies are listed in Table 3.1.

Table 3.1: Descriptive list of congenital anomalies by system (ICD-11)

System	Abnormality
Nervous system	Microcephaly, spina bifida, macrocephaly, ventriculomegaly, brachycephaly, holoprosencephaly, carpus callosum dysgenesis, myelomeningocele, septo-optic dysplasia, scaphocephaly, cranial nerve palsy, cerebral palsy
Eyes, eyelid, lacrimal apparatus	Hearing loss, Microphthalmia, epibulbar dermoid, congenital cataract, coloboma, congenital nystagmus
Ear	Microtia, anotia, preauricular skin tag, low set ears, external auditory canal atresia
Face, mouth or teeth	Micrognathia, retrognathia, glossoptosis, ankyloglossia, macrostomia, premaxilla agenesis, flat nasal bridge, facial skin tags, hemifacial microsomia
Respiratory system	Laryngomalacia, choanal atresia, tracheomalacia, tracheoesophageal fistula, single nasal cavity
Circulatory system	Ventricular septal defect, Atrial septal defect, Tetralogy of Fallot, Patent ductus arteriosus, Patent foramen ovale, Cavernoma, Tricuspid atresia, Pulmonary arterial stenosis
Diaphragm, abdominal wall or umbilical cord	Inguinal hernia, exomphalos, umbilical hernia, Morgagni hernia
Digestive tract	Anorectal malformation, Hirschsprung disease
Liver, biliary tract, pancreas or spleen	Duodenum atresia
Urinary system	Ectopic kidney, single kidney, duplex kidney, polycystic kidney, unilateral renal agenesis
Genital system	Bifid scrotum, hypospadias, undescended testes,
Breast	Hypermastia
Skeleton	Craniosynostosis, midface hypoplasia, frontal bossing, hypertelorism, scoliosis, kyphoscoliosis, pectus excavatum, talipes equinovarus, arthrogryposis, syndactyly, polydactyly, oligodactyly, clinodactyly, phocomelia, camptodactyly, short limbs, amniotic band constriction, limb contractures
Skin	Café au lait spot
Endocrine system	Thyroid dysgenesis

iv. The age of primary lip and palate repair conducted was recorded and categorised according to the treatment timeline used in the Combined Cleft Clinic, Faculty of Dentistry, Universiti Malaya (Appendix B).

The treatment timeline protocol was adapted from the American Cleft Palate-Craniofacial Association (ACPA) recommendation for cleft/lip palate surgery. ("Parameters For Evaluation and Treatment of Patients With Cleft Lip/Palate or Other Craniofacial Differences," 2018)

The primary lip and palate repair timing was categorised based on the following:

- Primary lip repair: ≤ 6 months or > 6 months.
- Primary palate repair- ≤ 18 months or > 18 months.

v. Complications of primary lip and palate repair were collected and divided into:

a) General complications
    - Duration of hospital stay
    - Admission into Paediatric Intensive Care Unit (PICU)

b) Perioperative complications consist of any event of complications that occur during the following period
    - Preoperative
        - Difficult intubation with desaturation episode
    - Intraoperative
        - Recurrent stridor
        - Endotracheal tube dislodged
        - Dislodged throat pack

- Postoperative
    - Sepsis
    - Wound dehiscence
    - Fitting episodes
    - Eye swelling
    - Oral ulcers
    - Bleeding from the surgical site
    - Pressure sore
    - Bronchospasm
    - Bronchopneumonia
    - Pyrexia

3.3 Data Analysis

After data collection, descriptive statistical analysis was conducted to establish frequencies, percentages and possible relationships between the variables included in the study. Chi-square test and Fisher's exact test were performed to determine the significant association between the age of primary lip and palate repair in syndromic and nonsyndromic orofacial cleft patients. P-value ≤ 0.05 was taken as significant. All data were analysed using SPSS version 29.

3.4 Ethical Approval

Ethical approval for this study was obtained from the Medical Ethics Committee, Faculty of Dentistry, Universiti Malaya, on the 26th of August 2021 (Ethics Committee/IRB Reference Number: DF OS2113/0054(L) (Appendix A).

CHAPTER 4: RESULTS

4.1 Demographic Data

The total number of patients in the Combined Cleft Clinic from the year 2000 to the year 2020 with complete records was 676. Most were nonsyndromic, with 599 patients (88.6%), while the number of syndromic patients was 77 (11.4%). The total number of patients according to gender was 332 (49.1%) for males and 344 (50.9%) for females, with the male to female ratio of 1:1. Among syndromic patients, 36 (46.8%) were male and 41 (53.2%) were female. Meanwhile, for nonsyndromic patients, 296 (49.4%) were male, and 303 (50.6%) were female. The ratio of male to female in the syndromic group was 1:1.3, while in the nonsyndromic group was 1:1.

Overall racial distribution among orofacial cleft patients, 470 (69.5%) were Malays, 143 (21.2%) were Chinese, 42 (6.2%) were Indian, 3 (0.4%) were Bumiputera (Sabah/ Sarawak), and 18 (2.7%) were other races. Malay patients were the majority of attendees in the Combined Cleft Clinic for both nonsyndromic and syndromic groups, accounting for 424 (70.8%) and 46 (59.7%), respectively. The Chinese patients were the second most common attendees, with 122 (20.4%) in the nonsyndromic and 21 (27.3%) in the syndromic group. Meanwhile, the Indian patients from nonsyndromic and syndromic groups accounted for 33 (5.5%) and 9 (11.7%), respectively. However, no Bumiputera (Sabah/ Sarawak) patients were in the syndromic orofacial cleft patients (Table 4.1).

Table 4.1: Demographic data of syndromic and nonsyndromic orofacial cleft patients in Combined Cleft Clinic, Faculty of Dentistry, Universiti Malaya

Variables		Patient, n (%)		Total, n (%)
		Nonsyndromic	Syndromic	
		599 (88.6)	77 (11.4)	676
Gender	Male	296 (49.4)	36 (46.8)	332 (49.1)
	Female	303 (50.6)	41 (53.2)	344 (50.9)
Race	Malay	424 (70.8)	46 (59.7)	470 (69.5)
	Chinese	122 (20.4)	21 (27.3)	143 (21.2)
	Indian	33 (5.5)	9 (11.7)	42 (6.2)
	Bumiputera (Sabah/Sarawak)	3 (0.5)	0	3 (0.4)
	Others	17 (2.8)	1 (1.3)	18 (2.7)

4.2 Prevalence of Syndromes and Congenital Anomalies associated with Orofacial Cleft

A total of 30 different types of syndromes were identified from the syndromic patients attending the Combined Cleft Clinic. The Pierre Robin sequence has the highest prevalence of syndrome associated with orofacial cleft patients, with 29 patients (37.66%). Notably, the Pierre Robin sequence is also part of other syndromes. The analysis done revealed patients with Stickler Syndrome, Beckwith-Wiedemann Syndrome, Goldenhar Syndrome, Mobius syndrome and other chromosomal disorders (abnormal Chromosome 9, partial trisomy 14) are associated with Pierre Robin Sequence. Syndromes related to chromosomal aberrant or abnormality were also identified, for example, 3p Duplication, 4q12q21.21 Deletion, 6q14.1 Deletion, Isochromosome 8q10, and 7q21.11q21.3 Deletion syndromes. Other syndromes associated with orofacial cleft included Down, Treacher Collin, CHARGE, DiGeorge, and Crouzon Syndrome (Table 4.2).

Table 4.2: Frequency of syndromes associated with Orofacial Cleft patients in Combined Cleft Clinic, Faculty of Dentistry, Universiti Malaya

Syndromes	n	%
3p Duplication Syndrome	1	1.30
4q12q21.21 Deletion Syndrome	1	1.30
6q14.1 Deletion Syndrome	1	1.30
Amniotic Band Sequence	3	3.90
Beckwith-Wiedemann Syndrome, Pierre Robin Sequence	1	1.30
Caudal Regression Syndrome	1	1.30
Charge Syndrome	2	2.60
Isochromosome 8q10	1	1.30
Chromosome 7q21.11q21.3 Deletion Syndrome	1	1.30
Crouzon Syndrome	1	1.30
Dandy-Walker Syndrome	1	1.30
DiGeorge Syndrome	2	2.60
Down Syndrome	5	6.49
Dandy-Walker Syndrome	1	1.30
Goldenhar Syndrome	3	3.90
Goldenhar Syndrome, Vacterl Association	1	1.30
Kabuki Syndrome	1	1.30
Med 13 L Syndrome	1	1.30
Mobius Syndrome, Pierre Robin Sequence	1	1.30
Noonan Syndrome	1	1.30
Ogden Syndrome	1	1.30
Pierre Robin Sequence	29	37.66
Pierre Robin Sequence, Abnormal Chromosome 9	1	1.30
Pierre Robin Sequence, Goldenhar Syndrome	1	1.30
Pierre Robin Sequence, Partial Trisomy 14 Syndrome	1	1.30
Pierre Robin Sequence, Stickler Syndrome	2	2.60
Robinow Syndrome	1	1.30
Rubinstein Taybi Syndrome	1	1.30
Russel Silver Syndrome	1	1.30
Treacher Collins Syndrome	5	6.49
Vacterl Association	2	2.60
Van Der Woude Syndrome	1	1.30
Wolf Hirchon Syndrome	1	1.30
Total	77	

The number of orofacial cleft patients with and without congenital anomalies was 143 (21.2%) and 533 (78.8%), respectively. Congenital anomalies were highly prevalent in the syndromic orofacial cleft group, with 76 patients (98.7%). Compared to the nonsyndromic group, only 67 patients (11.2%) had associated congenital anomalies (Table 4.3).

Overall, the circulatory system anomalies showed the highest frequency with 22.3%, followed by face, mouth or teeth with 20.1%, ear and skeleton with 12.4% and the nervous system anomalies with 7.8%. The face, mouth or teeth (22.2%) was the most commonly associated congenital anomaly in syndromic orofacial cleft patients, followed by circulatory system (19.0%), ear (15.3%) and skeletal (11.1%) anomalies. However, in the nonsyndromic group, the circulatory system (28.7%) has the highest occurrence, followed by face, mouth or teeth (16.0%) and skeleton (14.9%) anomalies (Table 4.4).

Table 4.3: Frequency of congenital anomalies in orofacial cleft patients in Combined Cleft Clinic, Faculty of Dentistry, Universiti Malaya

Variable	Patient, n (%)		Total
	Nonsyndromic	Syndromic	
With congenital anomaly	67 (11.2)	76 (98.7)	143 (21.2%)
Without congenital anomaly	532 (88.8)	1 (1.3)	533 (78.8%)

Table 4.4: Occurrence of congenital anomalies in syndromic and nonsyndromic orofacial cleft patients in Combined Cleft Clinic, Faculty of Dentistry, Universiti Malaya

Structural Developmental Anomaly (ICD-11)	Nonsyndromic	Syndromic	Total, n (%)
Nervous system	10 (10.6)	12 (6.3)	22 (7.8)
Eyes, eyelid, lacrimal apparatus	3 (3.2)	13 (6.9)	16 (5.7)
Ear	6 (6.4)	29 (15.3)	35 (12.4)
Face, mouth or teeth	15 (16.0)	42 (22.2)	57 (20.1)
Respiratory system	4 (4.3)	18 (9.5)	22 (7.8)
Circulatory system	27 (28.7)	36 (19.0)	63 (22.3)
Diaphragm, abdominal wall or umbilical cord	3 (3.2)	2 (1.1)	5 (1.8)
Digestive tract	1 (1.1)	5 (2.6)	6 (2.1)
Liver, biliary tract, pancreas or spleen	-	1 (0.5)	1 (0.5)
Urinary system	3 (3.2)	4 (2.1)	7 (2.5)
Genital system	6 (6.4)	3 (1.6)	9 (3.2)
Breast	1 (1.1)	1 (0.5)	2 (0.7)
Skeleton	14 (14.9)	21 (11.1)	35 (12.4)
Skin	-	2 (1.1)	2 (0.7)
Endocrine system	1 (1.1)	-	1 (0.4)

4.3 Types of cleft associated with syndromic and nonsyndromic orofacial cleft patients

The types of clefts analysed in the study include Bilateral Cleft Lip and Palate, Unilateral Cleft Lip and Palate, Cleft Lip, Cleft Lip and Alveolus, Cleft Palate, Submucous Cleft, and Facial Cleft. The most common types of cleft diagnosed from patients attending Combined Cleft Clinic were unilateral cleft lip and palate 244 (36.1%), followed by cleft palate 163(24.1%) and bilateral cleft lip and palate 122(18 %). The least common types of cleft diagnosed were facial cleft 16(2.4%) and submucous cleft 9(1.3%).

The highly prevalent cleft subtype diagnosed in the syndromic group was cleft palate with 52 patients (67.5 %), followed by bilateral cleft lip and palate with ten patients (13.0%) and unilateral cleft lip and palate with eight patients (10.4%). For the nonsyndromic group, unilateral cleft lip and palate were the common diagnoses with 236 patients (39.4%), followed by bilateral cleft lip and palate with 112 patients (18.7%) and cleft palate with 111 patients (18.5). Submucous cleft was the least common cleft subtype in the nonsyndromic and syndromic groups, accounting for eight patients (1.3%) and one patient (1.3%), respectively (Table 4.5).

Table 4.5: Types of cleft distribution in syndromic and nonsyndromic orofacial cleft patients in Combined Cleft Clinic, Faculty of Dentistry, Universiti Malaya

Types of cleft	Patient, n (%)		Total
	Nonsyndromic	Syndromic	
Bilateral cleft lip and palate	112 (18.7)	10 (13.0)	122 (18.0)
Unilateral Cleft Lip and palate	236 (39.4)	8 (10.4)	244 (36.1)
Cleft lip	45 (7.5)	1 (1.3)	46 (6.8)
Cleft lip and alveolus	73 (12.2)	3 (3.9)	76 (11.2)
Cleft palate	111 (18.5)	52 (67.5)	163 (24.1)
Submucous cleft	8 (1.3)	1 (1.3)	9 (1.3)
Facial cleft	14 (2.3)	2 (2.6)	16 (2.4)

4.4 Age of primary lip and palate repair

The overall number of patients who underwent primary lip repair in ≤ 6 months is 349 (69.0%) and 114 (23.0%) in > 6 months. Similarly, for primary palate repair,434 (78.2%) was done in ≤ 18 months and 66 (11.9 %) was done in > 18 months. The total number of patients whose age of surgery was not recorded was 41 (8.0%) for primary lip repair and 55(9.9%) for primary palate repair.

For the nonsyndromic group, 340 patients (70.8%) underwent primary lip repair at the age of ≤ 6 months and 103 (21.5%) at the age of > 6 months. Meanwhile, 393 (81.7%) patients underwent primary palate repair at ≤ 18 months and 38 patients (7.9%) at the age of > 18 months.

It can be observed, that in the syndromic group, nine patients (37.5%) underwent primary lip repair at the age of ≤ 6 months, and 11 patients (45.8%) at the age of > 6 months. Meanwhile, 41 patients (55.4 %) underwent primary palate repair at ≤ 18 months and 28 patients (37.8%) at > 18 months.

For the age of primary lip repair, Fisher's exact test reveals a statistically significant difference between the groups for the category of ≤ 6 months (p-value = 0.003). However, no significant difference is observed for the category of > 6 months. For the age of primary palatal repair, the Chi-square test shows a statistically significant difference between the groups for the age category of ≤ 18 months (p-value <0.001) but not for the category of >18 months (Table 4.6).

Table 4.6: Age group distribution of syndromic orofacial cleft patients undergoing primary lip and palate repair

Types of Surgery	Age (months)	Patient, n (%)		Total	p-value
		Nonsyndromic	Syndromic		
Primary lip repair	≤ 6 months	340 (70.8)	9 (37.5)	349 (69.0)	0.030
	> 6 months	103 (21.5)	11 (45.8)	114 (23.0)	
The age of primary lip repair was not recorded		37 (7.7)	4 (16.7)	41 (8.0)	
Primary palate repair	≤ 18 months	393 (81.7)	41 (55.4)	434 (78.2)	< 0.001
	> 18 months	38 (7.9)	28 (37.8)	66 (11.9)	
The age of primary palate repair was not recorded		50(10.4)	5(6.8)	55 (9.9)	

4.5 Complications in syndromic patients undergoing primary lip and palate repair

The primary lip and palate repair complications in syndromic patients were divided into general and perioperative complications. For the general complications, the most extended admission was 42 days. The regular period for patient stays in the hospital was three and four days, with occurrences of 13 and 10, respectively. Only five patients needed PICU admission after primary surgery (Table 4.7). Perioperative complications occurred in 12 patients, totalling 20 events. It can be observed that most complications occur in the postoperative period (65%), which include pyrexia, bronchopneumonia, sepsis and bronchospasm. During the pre and intraoperative period, intubation issues were apparent. Two patients had difficult intubation with desaturation episodes, and one had dislodgement of the endotracheal tube (Table 4.8).

Table 4.7: General complications of syndromic orofacial cleft patients undergoing primary lip and palate repair

Hospital stay	Duration (days)	n
	3	13
	4	10
	5	5
	7	2
	8	1
	17	1
	42	1
	No available information	44
PICU admission	Yes	5
	No	28
	No available information	44

Table 4.8: Perioperative complications of syndromic orofacial cleft patients undergoing primary lip and palate repair

Period	Complication	n (%)
Preoperative	Difficult intubation with desaturation episode	2 (10%)
Intraoperative	Recurrent stridor	3 (15%)
	Endotracheal tube dislodged	1 (5%)
	Dislodged throat pack	1 (5%)
Postoperative	Sepsis	1 (5%)
	Wound dehiscence	1 (5%)
	Fitting episodes	1 (5%)
	Left eye swelling	1 (5%)
	Oral ulcers	1 (5%)
	Bleeding from the surgical site	1 (5%)
	Pressure sore	1 (5%)
	Bronchospasm	1 (5%)
	Bronchopneumonia	2 (10%)
	Pyrexia	3 (15%)

CHAPTER 5: DISCUSSION

This study is a 20-year retrospective review of patients attending our centre, with the acquisition of data regarding managing syndromic orofacial cleft patients. The Combined Cleft Clinic, Faculty of Dentistry, Universiti Malaya, is a tertiary-care, referral, teaching hospital and one of the earliest multidisciplinary cleft care clinic established in Malaysia. To the best of our knowledge, the present study is the first to explore the prevalence of congenital anomalies, syndromes associated with orofacial cleft, the timing of primary lip and palate repair and the complications that occur.

A significant number of CL/P cases (70%) is categorised as nonsyndromic, meaning the clefts present with no additional anomalies (Stanier & Moore, 2004). Hadadi et al. (2017), conducted a retrospective study in a tertiary centre in Riyadh, Saudi Arabia and the result showed 81% of orofacial cleft were nonsyndromic, and only 19% were syndromic. Meanwhile, through an observational study in Berlin, Germany done by Bartzela et al. (2020), 90.8% of their patients were nonsyndromic, and only 9.2% were syndromic. It is comparable with the present study, which showed 88.6% of the patients were nonsyndromic, and patients diagnosed with syndromes were 11.4%.

More than 275 syndromes have been discovered in which orofacial cleft is the primary symptom, and these are caused by mutations at a single genetic locus, chromosomal abnormalities, or teratogens. Seventy-five percent of described syndromes have a known genetic cause, including hundreds of syndromes resulting from Mendelian inheritance at a single genetic locus.(Leslie & Marazita, 2013).

Our study showed Pierre Robin sequence is the most highly associated with orofacial cleft, and interestingly it also occurs as part of other syndromes like Stickler syndrome, Beckwith-Wiedemann syndrome and Goldenhar syndrome. This observation differs from

previous papers that reported Van Der Woude syndrome as the most common; in our centre, only one case was recorded in the past 20 years (Dixon et al., 2011; Jugessur & Murray, 2005; Zucchero et al., 2004). Another epidemiological study in Colombia revealed that Aarskog-Scott syndrome has a higher prevalence among syndromic orofacial cleft forms (Arias Urueña et al., 2015). Aarskog-Scott syndrome is due to mutations of the FGD1 gene. It is clinically characterized by facial dysmorphism, short stature, brachydactyly and genital anomalies (Aarskog, 1970; Hoffman et al., 2007). Other studies showed a lower prevalence of this syndrome due to highly variable phenotypic features, making the diagnosis difficult even though the clinical manifestation and diagnostic criteria are well established (Orrico et al., 2007; Zou et al., 2011). However, according to Hadadi et al. (2017) and Bartzela et al. (2020), the Pierre Robin Sequence is the most common entity associated with orofacial cleft patients. Their findings were consistent with our current study. The Pierre Robin sequence (PRS) is characterised by the clinical triad of congenital micrognathia, glossoptosis, and airway obstruction, with the variable addition of a cleft palate. When this combination of observations arises without other congenital anomalies, it is termed isolated PRS; however, PRS numerous times finds itself a component of a more complex syndromic picture. This phenotypic heterogeneity is the result of a combination of genetic, mechanical, and environmental disruptions(Hsieh & Woo, 2019). Between 26% and 83% of PRS diagnoses are part of a syndrome, most frequently Stickler syndrome, 22q11.2 Deletion Syndrome, Treacher Collins syndrome, and Campomelic Dysplasia, among others(Gomez-Ospina & Bernstein, 2016; Jakobsen et al., 2007). Stickler syndrome, a connective tissue disorder affecting collagen metabolism, is diagnosed in 11% to 18% of PRS patients(Tan et al., 2013).

The frequency of orofacial cleft patients with associated congenital anomalies in our studies is 21.2%. The result is comparable with other studies, which reported 21%(Hadadi

et al., 2017; Milerad et al., 1997) and 27.8% (Bartzela et al., 2021). Literature reports incidence rates of associated anomalies of other organs in orofacial cleft patients ranging from 3% to 72%(Shprintzen et al., 1985). However, our study showed a higher percentage of associated congenital anomalies compared to other studies conducted in Asia 1.5% (Yi et al., 1999), 14.3%(Rawashdeh & Jawdat Abu-Hawas, 2008), 14.8% (Sekhon et al., 2011) and 18%(Al Omari & Al-Omari, 2004).

The reported literature does not explicitly recognise the associated congenital anomalies in syndromic orofacial cleft patients. Our study revealed the face, mouth, or teeth were the most common congenital anomalies in syndromic orofacial cleft patients, with 42 patients (22.2%). Face, mouth, or teeth abnormalities include micrognathia, retrognathia, ankyloglossia, macrostomia, premaxilla agenesis, facial skin tags and hemifacial microsomia. Multiple studies investigating the association of congenital anomalies have been conducted and revealed diverse results. Variations in the reported frequency of associated anomalies among cleft patients have long been attributed to methodological factors. The variations may be due to (1) case definition and inclusion/exclusion criteria; (2) length of time after birth that cases are examined; (3) variability in clinical expression of associated anomalies; (4) knowledge and technology available to produce syndrome delineation; (5) selection of patients, sources of ascertainment, and sample size; and (6) actual population differences and changes in frequency over time (Wyszynski et al., 2006). A study in India showed facial anomalies were most frequently detected in nonsyndromic orofacial cleft patients (Sekhon et al., 2011).

Meanwhile, a single-centre retrospective study in Saudi Arabia showed that congenital heart anomalies (60%) were commonly associated anomalies in orofacial cleft patients (Hadadi et al., 2017). Musculoskeletal anomalies have a higher frequency, according to a

study in Berlin with 27.7% (Bartzela et al., 2021) and in Colombia with 51.4% (Arias Urueña et al., 2015). This may result from the actions of several genes that serve a crucial role in the development of connective tissue(Hwang et al., 1998; Mossey & Modell, 2012).

No data on orofacial cleft patients with associated syndromes and congenital anomalies in Malaysia was available. One epidemiological study conducted in a district in Perak regarding birth defects revealed the incidence of major birth defects is 14.3 per 1000 births and 22.5% of infants born with multiple congenital anomalies. The primary organ systems involved in isolated birth defects were cardiovascular, cleft lip and palate, clubfeet, and central nervous system (CNS) (including neural tube defects) (Thong et al., 2005). According to the Malaysian Neonatal Registry Report 2008, 16.8% of infants had congenital anomalies. 28% was the syndromic diagnosis. There were 1353 patients with nonsyndromic anomalies (isolated or multiple congenital anomalies). The most common organ system affected was the cardiovascular system, followed by cleft lip and palate, gastrointestinal tract (GIT) anomalies and central nervous system (CNS) anomalies. The incidence of cleft anomaly is 1.1/1000 livebirths, and cleft lip and palate are highly prevalent.

Unilateral cleft lip and palate (36.1%) is the most common cleft subtypes amongst patients attending Combined Cleft Clinic, followed by cleft palate (24.1%). This result is lower than Bartzela et al. (2020), who reported 57.9% of patients with cleft lip and palate and 25.2% with cleft palate in their study. Sekhon et al. (20201) demonstrated that 41% of their patients have unilateral cleft lip and palate, followed by cleft lip and/or alveolus with 33%.

In syndromic patients, cleft palate is highly prevalent, with 67.5%. This finding is consistent with Bartzela et al. (2017), who reported a high frequency of patients with cleft

palate (79%) having associated syndrome. Cleft palate can be categorised into two groups: (1) syndromic isolated cleft palate (CPO), which is related to additional structural abnormalities occurring outside the region of the cleft or with a syndrome with a known genetic aetiology, and (2) nonsyndromic isolated cleft palate is an isolated condition not connected to any identifiable anomalies (Mai et al., 2014; Watkins et al., 2014). The frequency of oral clefts with additional anomalies is greater for isolated cleft palate (CPO) than CL/P(Mossey et al., 2009). About fifty percent of isolated cleft palate (CPO) are associated with another malformation syndrome, whereas less than fifteen percent of CL/P are (Mossey & Ee, 2003).

Interestingly, submucous cleft palate was the least common subtype diagnosed in both syndromic and nonsyndromic orofacial cleft patients, with a percentage of 1.3% for both groups. Submucous cleft palate often presents with distinct anatomical features, including a bifid uvula, a bony notch in the posterior part of the hard palate, and a muscle diastasis also known as 'zona pellucida' or translucent zone. Despite these anatomical features, misdiagnosed is possible because it can present as an occult submucous cleft palate (Calnan, 1954; Kaplan, 1975). A retrospective review of the submucous cleft palate showed mean age of diagnosis is 3.9 years. Most of the patients had symptomatic complaints, including hypernasality, problems in articulation, conductive hearing loss and swallowing problems. The successful treatment for hypernasality is pharyngoplasty (ten Dam et al., 2013).

Most nonsyndromic orofacial cleft patients managed to get their primary lip and palate repair following the recommended timing within 6 and 18 months old, respectively. The timing of primary cleft repair in Combined Cleft Clinic, Faculty of Dentistry, Universiti Malaya, aligns with other centre recommendations. For example, The American Cleft Palate-Craniofacial Association recommended primary lip repair within the first 12

months and primary palatal closure by 18 months("Parameters For Evaluation and Treatment of Patients With Cleft Lip/Palate or Other Craniofacial Differences," 2018).

Only 35.5% of syndromic patients managed to get primary lip repair at ≤ 6 months. The syndromic patient underwent delayed primary lip repair, which might be due to underlying comorbidities that need to be treated, such as poor weight gain, congenital heart problems or airway related issues that make the surgical procedure considered high risk for them. Fillies et al. (2007) reported a direct correlation between the risk of complications to body weight in cleft repair. For patients weighing between 4 and 6 kg, 54% were found to have complications compared to patients with a body weight of more than 8kg, have 26% of complications during cleft repair. The "rule of 10" can be implied even though its validity is controversial considering the advancement in paediatric anaesthesia and surgical technique. It can be used as a guide before the commencement of primary lip repair, where the patients should be ten weeks old, attain the weight of 10 pounds and have a Hemoglobin of 10g/dL (Millard, 1976).

For primary palatal repair in syndromic patients, 55.4% had received surgery within standard timing. This can be because some of the medical issues have been resolved as the patient grows. With good support from our anaesthetic and paediatric team, the patient can be safely operated under general anaesthesia. Most cleft surgeons advocate the primary palate repair to be performed between the ages of 9 and 18 months. The timing of repair for cleft palate is controversial. Early palate closure would cause inhibition of facial growth, but if it is delayed, substantial speech impairments to the patients are apparent (Burg et al., 2016). A 2007 survey of 306 American cleft surgeons revealed that 96% perform one-stage repairs, and 85% conduct palate surgery between six and twelve months. There is evidence that palate repair is not beneficial for children over the age of seven, as significant speech abilities have already developed and altering the anatomy at

this stage may hinder speech development. Before an infant's first palate surgery, early interventions such as nasoalveolar moulding, presurgical orthopaedics, external taping, and gingivoperiosteoplasty aim to minimise the number of necessary surgeries and optimise surgical outcomes by repositioning bony and soft tissue structures(Hopper et al., 2007). A systematic review was conducted to find clinical decisions based on randomised controlled trials for cleft repair. Still, the results revealed few randomised controlled trials regarding cleft treatment and fewer related to surgical repair of the deformity. The authors also found no study in the selected samples specifically analysed cleft patients with a syndrome or congenital anomalies(de Ladeira & Alonso, 2012).

Only 12 patients experience complications following the primary lip and palate repair surgery. Generally, most of our syndromic patients had to be admitted for three to four days following their primary lip and palate repair. However, the recorded extended admission was 42 days, and where the patient developed stridor intraoperative and had to be admitted into PICU for eight days before could be safely extubated and transferred to the regular ward. The patient was also diagnosed with bronchopneumonia postoperatively and needed intravenous antibiotic therapy, which prolonged the hospital stay. The airway issue is the common pre and intraoperative complication from our findings. This correlates with a prospective study of 800 paediatric patients undergoing repair of cleft lip and palate to identify the predictors of laryngoscopy difficulty. The incidence of problematic laryngoscopy (Cormack and Lehane grades III and IV) was 3.0% in patients with a unilateral cleft lip, 45.8% in patients with bilateral cleft lips, and 34.6% in patients with retrognathia. Laryngoscopy becomes simpler with age (66.1% of patients with a difficult laryngoscopy were younger than six months). As extensive clefts, retrognathia, and an age of under six months are associated with challenging laryngoscopy, these conditions must be considered when planning the anaesthetic technique(Gunawardana, 1996). Another study showed emergence and maintenance of a stable upper airway

throughout intubation, ventilation, and extubation was associated with a high incidence of complications such as tube dislocation, difficult intubation, low oxygenation, reintubation, laryngospasm and bronchospasm (Fillies et al., 2007). Our study's most common postoperative complication is pyrexia, with a frequency of 15%. Another study on complications of primary cleft repair demonstrated that 17 cases develop pyrexia postoperatively, and it can be due to drug fever, preoperative chronic respiratory tract infection, and wound infection(Zhang et al., 2014).

5.1 Limitations of study

i. This is a retrospective study where the patient's records were traced back 20 years. Incomplete records were unavoidable, especially if the patient was not actively managed for more than seven years. Their records might be disposed of.

ii. Poor record keeping was encountered during data collection, as some clinical information could not be extracted from the patient's records.

iii. This is a single-centre study. Thus, results should be interpreted cautiously as it cannot be generalised to the entire population.

5.2 Recommendations

i. A multicenter study should be conducted to get the epidemiological data of orofacial cleft patients. Thus, the prevalence of cleft subtypes, associated syndromes, congenital anomalies, details and complications of surgical procedures can be assessed, and a suitable multidisciplinary facility can be set up based on the data.

ii. A good cleft database or registry should be established in regard to the orofacial cleft patient where all the teams involved in managing cleft cases like Paediatric, Otorhinolaryngology, Plastic Surgery, Obstetrics and Gynaecology were able to key in all the relevant clinical information. So that future research can be conducted relevant to the orofacial cleft population.

CHAPTER 6: CONCLUSION

This study showed that most orofacial cleft patients in the Combined Cleft Clinic, Faculty of Dentistry, Universiti Malaya were nonsyndromic (88.6%). Only 11.4% were syndromic. Unilateral cleft lip and palate were the most common cleft subtypes in overall orofacial cleft patients. Cleft palate is highly associated with syndromic patients meanwhile in nonsyndromic patients unilateral cleft lip and palate is highly prevalent. Pierre Robin Sequence is the most commonly diagnosed syndrome.

Circulatory system anomalies like atrial and ventricular septal defects are highly associated with orofacial cleft patients. Face, mouth and teeth anomalies are highly prevalent in syndromic patients. Thus, routine screening for congenital abnormalities should be carried out in all orofacial cleft patients, especially in syndromic patients. Most nonsyndromic patients underwent primary lip repair within 6 months of age and palate repair within 18 months of age. For syndromic patients, most had primary palate repair within 18 months of age. Significant delay was noted in primary lip repair for syndromic patients. The complications after primary lip and palate repair in syndromic patients are commonly related to airway issues, and in the postoperative period, pyrexia is likely to occur.

REFERENCES

Aarskog, D. (1970). A familial syndrome of short stature associated with facial dysplasia and genital anomalies. *J Pediatr*, *77*(5), 856-861. https://doi.org/10.1016/s0022-3476(70)80247-5

Abyholm, F. E. (1978a). Cleft lip and palate in a Norwegian population. II. A numerical study of 1555 CLP-patients admitted for surgical treatment 1954-75. *Scand J Plast Reconstr Surg*, *12*(1), 35-43. https://doi.org/10.3109/02844317809010478

Abyholm, F. E. (1978b). Cleft lip and palate in Norway. I. Registration, incidence and early mortality of infants with CLP. *Scand J Plast Reconstr Surg*, *12*(1), 29-34. https://doi.org/10.3109/02844317809010477

Adesina, O. A., Efunkoya, A. A., Omeje, K. U., & Idon, P. I. (2016). Postoperative complications from primary repair of cleft lip and palate in a semi-urban Nigerian teaching hospital. *Nigerian Medical Journal: Journal of the Nigeria Medical Association*, *57*(3), 155. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4924396/pdf/NMJ-57-155.pdf

Aguilella, C., Dubourg, C., Attia-Sobol, J., Vigneron, J., Blayau, M., Pasquier, L., Lazaro, L., Odent, S., & David, V. (2003). Molecular screening of the TGIF gene in holoprosencephaly: identification of two novel mutations. *Hum Genet*, *112*(2), 131-134. https://doi.org/10.1007/s00439-002-0862-8

Al Omari, F., & Al-Omari, I. (2004). Cleft lip and palate in Jordan: birth prevalence rate. *The Cleft Palate-Craniofacial Journal*, *41*(6), 609-612.

al-Gazali, L. I., Dawodu, A. H., Sabarinathan, K., & Varghese, M. (1995). The profile of major congenital abnormalities in the United Arab Emirates (UAE) population. *J Med Genet*, *32*(1), 7-13. https://doi.org/10.1136/jmg.32.1.7

Anyanwu, L.-J. C., Danborno, B., & Hamman, W. O. (2015). Birth prevalence of overt congenital anomalies in Kano Metropolis: overt congenital anomalies in the Kano. *Nature*, *220*(25.55), 58-97.

Arias Urueña, L., Briceño Balcazar, I., Martinez Lozano, J., Collins, A., & Uricoechea Patiño, D. A. (2015). Clinical aspects associated with syndromic forms of Orofacial Clefts in a Colombian population. *Colombia Médica*, *46*(4), 162-167.

Ashouri, S., Khorramkhorshid, H., & Ebadifar, A. (2021). Orofacial Closure Defects: Forty-Five Genes Associated Cleft Lip and Palate [Review Article]. *Precis Med Clin OMICS*, *1*(1), e115500. https://doi.org/10.5812/pmco.115500

Bartzela, T., Theuerkauf, B., Reichardt, E., Spielmann, M., & Opitz, C. (2021). Clinical characterization of 266 patients and family members with cleft lip and/or palate with associated malformations and syndromes. *Clin Oral Investig*, *25*(9), 5531-5540. https://doi.org/10.1007/s00784-021-03863-2

Benko, S., Fantes, J. A., Amiel, J., Kleinjan, D. J., Thomas, S., Ramsay, J., Jamshidi, N., Essafi, A., Heaney, S., Gordon, C. T., McBride, D., Golzio, C., Fisher, M., Perry,

P., Abadie, V., Ayuso, C., Holder-Espinasse, M., Kilpatrick, N., Lees, M. M., . . . Lyonnet, S. (2009). Highly conserved non-coding elements on either side of SOX9 associated with Pierre Robin sequence. *Nat Genet*, *41*(3), 359-364. https://doi.org/10.1038/ng.329

Bernheim, N., Georges, M., Malevez, C., De Mey, A., & Mansbach, A. (2006). Embryology and epidemiology of cleft lip and palate. *B-ent*, *2 Suppl 4*, 11-19.

Boo, N., & Arshad, A. (1990). A study of cleft lip and palate in neonates born in a large Malaysian maternity hospital over a 2-year period. *Singapore Med J*, *31*(1), 59-62.

Burdi, A. R. (2006). Developmental Biology and Morphogenesis of the Face, Lip and Palate. In S. Berkowitz (Ed.), *Cleft Lip and Palate* (pp. 3-12). Springer Berlin Heidelberg. https://doi.org/10.1007/3-540-30020-1_1

Burg, M. L., Chai, Y., Yao, C. A., Magee III, W., & Figueiredo, J. C. (2016). Epidemiology, etiology, and treatment of isolated cleft palate. *Frontiers in physiology*, *7*, 67.

Calnan, J. (1954). Submucous cleft palate. *Br J Plast Surg*, *6*(4), 264-282. https://doi.org/10.1016/s0007-1226(53)80060-3

Calzolari, E. (2007). Pier ini A, Astolfi G, Bianchi F, Neville AJ, Rivieri F. Associated anomalies in multi-malformed infants with cleft lip and palate: An epidemiologic study of nearly 6 million births in 23 EUROCAT registries. *Am J Med Genet A*, *143*, 528-537.

Cordero, D. R., Brugmann, S., Chu, Y., Bajpai, R., Jame, M., & Helms, J. A. (2011). Cranial neural crest cells on the move: their roles in craniofacial development. *Am J Med Genet A*, *155a*(2), 270-279. https://doi.org/10.1002/ajmg.a.33702

de Aguiar, P. K., Coletta, R. D., de Oliveira, A. M., Machado, R. A., Furtado, P. G., de Oliveira, L. A., de Aquino, S. N., Martelli-Junior, H., de Almeida Reis, S. R., Moreira, H. S., & Persuhn, D. C. (2015). rs1801133C>T polymorphism in MTHFR is a risk factor for nonsyndromic cleft lip with or without cleft palate in the Brazilian population. *Birth Defects Res A Clin Mol Teratol*, *103*(4), 292-298. https://doi.org/10.1002/bdra.23365

de Ladeira, P. R., & Alonso, N. (2012). Protocols in cleft lip and palate treatment: systematic review. *Plast Surg Int*, *2012*, 562892. https://doi.org/10.1155/2012/562892

Dixon, M. J., Marazita, M. L., Beaty, T. H., & Murray, J. C. (2011). Cleft lip and palate: understanding genetic and environmental influences. *Nat Rev Genet*, *12*(3), 167-178. https://doi.org/10.1038/nrg2933

Eaton, A. C., Marsh, J. L., & Pilgram, T. K. (1994). Does reduced hospital stay affect morbidity and mortality rates following cleft lip and palate repair in infancy? *Plast Reconstr Surg*, *94*(7), 911-915; discussion 916-918.

Farronato, G., Cannalire, P., Martinelli, G., Tubertini, I., Giannini, L., Galbiati, G., & Maspero, C. (2014). Cleft lip and/or palate. *Minerva Stomatol*, *63*(4), 111-126.

Fillies, T., Homann, C., Meyer, U., Reich, A., Joos, U., & Werkmeister, R. (2007). Perioperative complications in infant cleft repair. *Head Face Med*, *3*, 9. https://doi.org/10.1186/1746-160x-3-9

Francis-West, P., Ladher, R., Barlow, A., & Graveson, A. (1998). Signalling interactions during facial development. *Mech Dev*, *75*(1-2), 3-28. https://doi.org/10.1016/s0925-4773(98)00082-3

Gomella, T. L., Eyal, F. G., & Bany-Mohammed, F. (2020). Common Multiple Congenital Anomalies: Syndromes, Sequences, and Associations. In *Gomella's Neonatology: Management, Procedures, On-Call Problems, Diseases, and Drugs, 8e*. McGraw-Hill Education. accesspediatrics.mhmedical.com/content.aspx?aid=1168357540

Gomez-Ospina, N., & Bernstein, J. A. (2016). Clinical, cytogenetic, and molecular outcomes in a series of 66 patients with Pierre Robin sequence and literature review: 22q11.2 deletion is less common than other chromosomal anomalies. *Am J Med Genet A*, *170a*(4), 870-880. https://doi.org/10.1002/ajmg.a.37538

Graham, J. M., Jr. (2001). A recognizable syndrome within CHARGE association: Hall-Hittner syndrome. *Am J Med Genet*, *99*(2), 120-123. https://doi.org/10.1002/1096-8628(2000)9999:999<00::aid-ajmg1132>3.0.co;2-j

Gripp, K. W., Wotton, D., Edwards, M. C., Roessler, E., Ades, L., Meinecke, P., Richieri-Costa, A., Zackai, E. H., Massagué, J., Muenke, M., & Elledge, S. J. (2000). Mutations in TGIF cause holoprosencephaly and link NODAL signalling to human neural axis determination. *Nat Genet*, *25*(2), 205-208. https://doi.org/10.1038/76074

Gunawardana, R. H. (1996). Difficult laryngoscopy in cleft lip and palate surgery. *Br J Anaesth*, *76*(6), 757-759. https://doi.org/10.1093/bja/76.6.757

Guo, L., Elcioglu, N. H., Wang, Z., Demirkol, Y. K., Isguven, P., Matsumoto, N., Nishimura, G., Miyake, N., & Ikegawa, S. (2017). Novel and recurrent COL11A1 and COL2A1 mutations in the Marshall-Stickler syndrome spectrum. *Hum Genome Var*, *4*, 17040. https://doi.org/10.1038/hgv.2017.40

Hadadi, A. I., Al Wohaibi, D., Almtrok, N., Aljahdali, N., AlMeshal, O., & Badri, M. (2017). Congenital anomalies associated with syndromic and non-syndromic cleft lip and palate. *JPRAS Open*, *14*, 5-15. https://doi.org/https://doi.org/10.1016/j.jpra.2017.06.001

He, F., Xiong, W., Wang, Y., Matsui, M., Yu, X., Chai, Y., Klingensmith, J., & Chen, Y. (2010). Modulation of BMP signalling by Noggin is required for the maintenance of palatal epithelial integrity during palatogenesis. *Dev Biol*, *347*(1), 109-121. https://doi.org/10.1016/j.ydbio.2010.08.014

Hodgkinson, P. D., Brown, S., Duncan, D., Grant, C., McNaughton, A. M. Y., Thomas, P., & Mattick, C. R. (2005). MANAGEMENT OF CHILDREN WITH CLEFT

LIP AND PALATE: A REVIEW DESCRIBING THE APPLICATION OF MULTIDISCIPLINARY TEAM WORKING IN THIS CONDITION BASED UPON THE EXPERIENCES OF A REGIONAL CLEFT LIP AND PALATE CENTRE IN THE UNITED KINGDOM. *Fetal and Maternal Medicine Review*, *16*(1), 1-27. https://doi.org/10.1017/S0965539505001452

Hoffman, J. D., Irons, M., Schwartz, C. E., Medne, L., & Zackai, E. H. (2007). A newly recognized craniosynostosis syndrome with features of Aarskog-Scott and Teebi syndromes. *Am J Med Genet A*, *143a*(12), 1282-1286. https://doi.org/10.1002/ajmg.a.31780

Hopper, R. A., Cutting, C., & Grayson, B. (2007). Cleft lip and palate. *Grabb and Smith's Plastic Surgery. 6th Edition. Philladelphia: Lippincott Williams and Wilkins*, *201*.

Hsieh, S. T., & Woo, A. S. (2019). Pierre robin sequence. *Clinics in plastic surgery*, *46*(2), 249-259.

Hwang, S. J., Beaty, T. H., McIntosh, I., Hefferon, T., & Panny, S. R. (1998). Association between homeobox-containing gene MSX1 and the occurrence of limb deficiency. *Am J Med Genet*, *75*(4), 419-423.

Iordanskaia, T., & Nawshad, A. (2011). Mechanisms of transforming growth factor β induced cell cycle arrest in palate development. *J Cell Physiol*, *226*(5), 1415-1424. https://doi.org/10.1002/jcp.22477

Jakobsen, L. P., Ullmann, R., Christensen, S. B., Jensen, K. E., Mølsted, K., Henriksen, K. F., Hansen, C., Knudsen, M. A., Larsen, L. A., Tommerup, N., & Tümer, Z. (2007). Pierre Robin sequence may be caused by dysregulation of SOX9 and KCNJ2. *J Med Genet*, *44*(6), 381-386. https://doi.org/10.1136/jmg.2006.046177

Jugessur, A., & Murray, J. C. (2005). Orofacial clefting: recent insights into a complex trait. *Current opinion in genetics & development*, *15*(3), 270-278.

Kaplan, E. N. (1975). The occult submucous cleft palate. *Cleft Palate J*, *12*, 356-368.

Kingston, H. M. (2002). *ABC of clinical genetics*. London: BMJ Books.

Lacbawan, F., Solomon, B. D., Roessler, E., El-Jaick, K., Domené, S., Vélez, J. I., Zhou, N., Hadley, D., Balog, J. Z., Long, R., Fryer, A., Smith, W., Omar, S., McLean, S. D., Clarkson, K., Lichty, A., Clegg, N. J., Delgado, M. R., Levey, E., . . . Muenke, M. (2009). Clinical spectrum of SIX3-associated mutations in holoprosencephaly: correlation between genotype, phenotype and function. *J Med Genet*, *46*(6), 389-398. https://doi.org/10.1136/jmg.2008.063818

Lees, V. C., & Pigott, R. W. (1992). Early postoperative complications in primary cleft lip and palate surgery--how soon may we discharge patients from hospital? *Br J Plast Surg*, *45*(3), 232-234. https://doi.org/10.1016/0007-1226(92)90084-b

Leslie, E. J., & Marazita, M. L. (2013). Genetics of cleft lip and cleft palate. American Journal of Medical Genetics Part C: Seminars in Medical Genetics,

Li, B., Ma, L., Zhang, C., Zhou, Z., Yuan, H., Jiang, H., Pan, Y., & Tan, Q. (2018). Associations of genetic variants in endocytic trafficking of epidermal growth factor receptor super pathway with risk of nonsyndromic cleft lip with or without cleft palate. *Mol Genet Genomic Med*, *6*(6), 1157-1167. https://doi.org/10.1002/mgg3.497

Liao, Y. F., Prasad, N. K., Chiu, Y. T., Yun, C., & Chen, P. K. (2010). Cleft size at the time of palate repair in complete unilateral cleft lip and palate as an indicator of maxillary growth. *Int J Oral Maxillofac Surg*, *39*(10), 956-961. https://doi.org/10.1016/j.ijom.2010.01.024

Lilius, G. P. (1992). Clefts with associated anomalies and syndromes in Finland. *Scand J Plast Reconstr Surg Hand Surg*, *26*(2), 185-196. https://doi.org/10.3109/02844319209016011

Lohmander, A., Willadsen, E., Persson, C., Henningsson, G., Bowden, M., & Hutters, B. (2009). Methodology for speech assessment in the Scandcleft project--an international randomized clinical trial on palatal surgery: experiences from a pilot study. *Cleft Palate Craniofac J*, *46*(4), 347-362. https://doi.org/10.1597/08-039.1

Losee, J. E., Smith, D. M., Afifi, A. M., Jiang, S., Ford, M., Vecchione, L., Cooper, G. M., Naran, S., Mooney, M. P., & Serletti, J. M. (2008). A successful algorithm for limiting postoperative fistulae following palatal procedures in the patient with orofacial clefting. *Plast Reconstr Surg*, *122*(2), 544-554. https://doi.org/10.1097/PRS.0b013e31817d6223

Losken, H. W., van Aalst, J. A., Teotia, S. S., Dean, S. B., Hultman, S., & Uhrich, K. S. (2011). Achieving low cleft palate fistula rates: surgical results and techniques. *Cleft Palate Craniofac J*, *48*(3), 312-320. https://doi.org/10.1597/08-288

Lubinsky, M. S. (1994). Properties of associations: identity, nature, and clinical criteria, with a commentary on why CHARGE and Goldenhar are not associations. *Am J Med Genet*, *49*(1), 21-25. https://doi.org/10.1002/ajmg.1320490106

Mai, C. T., Cassell, C. H., Meyer, R. E., Isenburg, J., Canfield, M. A., Rickard, R., Olney, R. S., Stallings, E. B., Beck, M., Hashmi, S. S., Cho, S. J., & Kirby, R. S. (2014). Birth defects data from population-based birth defects surveillance programs in the United States, 2007 to 2011: highlighting orofacial clefts. *Birth Defects Res A Clin Mol Teratol*, *100*(11), 895-904. https://doi.org/10.1002/bdra.23329

Marcus, C. L., Brooks, L. J., Draper, K. A., Gozal, D., Halbower, A. C., Jones, J., Schechter, M. S., Ward, S. D., Sheldon, S. H., Shiffman, R. N., Lehmann, C., & Spruyt, K. (2012). Diagnosis and management of childhood obstructive sleep apnea syndrome. *Pediatrics*, *130*(3), e714-755. https://doi.org/10.1542/peds.2012-1672

Meng, P., Zhao, H., Huang, W., Zhang, Y., Zhong, W., Zhang, M., Jia, P., Zhou, Z., Maimaitili, G., Chen, F., Zhang, J., & Lin, J. (2019). Three GLI2 mutations combined potentially underlie non-syndromic cleft lip with or without cleft palate in a Chinese pedigree. *Mol Genet Genomic Med*, *7*(9), e714. https://doi.org/10.1002/mgg3.714

Meyers, A. D. (1993). *Biological basis of facial plastic surgery*. Thieme Medical Publishers.

Milerad, J., Larson, O., Hagberg, C., & Ideberg, M. (1997). Associated malformations in infants with cleft lip and palate: a prospective, population-based study. *Pediatrics*, *100*(2), 180-186.

Millard, D. R. (1976). *Cleft Craft: The Unilateral Deformity/D. Ralph Millard*. Little, Brown.

Minoux, M., & Rijli, F. M. (2010). Molecular mechanisms of cranial neural crest cell migration and patterning in craniofacial development. *Development*, *137*(16), 2605-2621. https://doi.org/10.1242/dev.040048

Mooney, M. (2008). Classification of orofacial clefting. *Comprehensive cleft care*, 21-33.

Moreira, H. S. B., Machado, R. A., Aquino, S. N. d., Rangel, A. L. C. A., Martelli Júnior, H., & Coletta, R. D. (2016). Epidemiological features of patients with nonsyndromic cleft lip and/or palate in Western Parana. *Brazilian Journal of Oral Sciences*, *15*(1), 39-44.

Mossey, P., & Ee, C. (2003). Global Registry and Database on Craniofacial Anomalies.

Mossey, P. A., Little, J., Munger, R. G., Dixon, M. J., & Shaw, W. C. (2009). Cleft lip and palate. *The Lancet*, *374*(9703), 1773-1785.

Mossey, P. A., & Modell, B. (2012). Epidemiology of oral clefts 2012: an international perspective. *Front Oral Biol*, *16*, 1-18. https://doi.org/10.1159/000337464

Nahai, F. R., Williams, J. K., Burstein, F. D., Martin, J., & Thomas, J. (2005). The management of cleft lip and palate: pathways for treatment and longitudinal assessment. Seminars in Plastic Surgery,

Noordhoff, M. S., Huang, C. S., & Lo, L. J. (1993). Median facial dysplasia in unilateral and bilateral cleft lip and palate: a subgroup of median cerebrofacial malformations. *Plast Reconstr Surg*, *91*(6), 996-1005; discussion 1006-1007.

Orrico, A., Galli, L., Obregon, M. G., de Castro Perez, M. F., Falciani, M., & Sorrentino, V. (2007). Unusually severe expression of craniofacial features in Aarskog-Scott syndrome due to a novel truncating mutation of the FGD1 gene. *Am J Med Genet A*, *143a*(1), 58-63. https://doi.org/10.1002/ajmg.a.31562

Pagon, R. A., Graham, J. M., Jr., Zonana, J., & Yong, S. L. (1981). Coloboma, congenital heart disease, and choanal atresia with multiple anomalies: CHARGE association. *J Pediatr*, *99*(2), 223-227. https://doi.org/10.1016/s0022-3476(81)80454-4

Panamonta, V., Msn, S., Panamonta, M., & Chowchuen, B. (2015). Global Birth Prevalence of Orofacial Clefts: A Systematic Review. *Journal of the Medical Association of Thailand = Chotmaihet thangphaet*, *98*, S11-21.

Parameters For Evaluation and Treatment of Patients With Cleft Lip/Palate or Other Craniofacial Differences. (2018). *The Cleft Palate Craniofacial Journal*, *55*(1), 137-156. https://doi.org/10.1177/1055665617739564

Pool, R., & Farnworth, T. K. (1994). Preoperative lip taping in the cleft lip. *Ann Plast Surg*, *32*(3), 243-249. https://doi.org/10.1097/00000637-199403000-00003

Qian, Y., Li, D., Ma, L., Zhang, H., Gong, M., Li, S., Yuan, H., Zhang, W., Ma, J., Jiang, H., Pan, Y., & Wang, L. (2016). TPM1 polymorphisms and nonsyndromic orofacial clefts susceptibility in a Chinese Han population. *Am J Med Genet A*, *170a*(5), 1208-1215. https://doi.org/10.1002/ajmg.a.37561

Rafiqdoost, Z., Rafiqdoost, A., Rafiqdoost, H., Hashemi, M., Khayatzadeh, J., & Eskandari-Nasab, E. (2014). Investigation of FGF1 and FGFR gene polymorphisms in a group of Iranian patients with nonsyndromic cleft lip with or without cleft palate. *Int J Pediatr Otorhinolaryngol*, *78*(5), 731-736. https://doi.org/10.1016/j.ijporl.2014.01.024

Rahimov, F., Jugessur, A., & Murray, J. C. (2012). Genetics of nonsyndromic orofacial clefts. *Cleft Palate Craniofac J*, *49*(1), 73-91. https://doi.org/10.1597/10-178

Rawashdeh, M. A., & Jawdat Abu-Hawas, B. (2008). Congenital associated malformations in a sample of Jordanian patients with cleft lip and palate. *J Oral Maxillofac Surg*, *66*(10), 2035-2041. https://doi.org/10.1016/j.joms.2008.01.009

Reardon, W., Winter, R. M., Rutland, P., Pulleyn, L. J., Jones, B. M., & Malcolm, S. (1994). Mutations in the fibroblast growth factor receptor 2 gene cause Crouzon syndrome. *Nat Genet*, *8*(1), 98-103. https://doi.org/10.1038/ng0994-98

Reynolds, K., Zhang, S., Sun, B., Garland, M. A., Ji, Y., & Zhou, C. J. (2020). Genetics and signalling mechanisms of orofacial clefts. *Birth Defects Res*, *112*(19), 1588-1634. https://doi.org/10.1002/bdr2.1754

Rodman, R. E., & Tatum, S. (2016). Controversies in the Management of Patients with Cleft Lip and Palate. *Facial Plast Surg Clin North Am*, *24*(3), 255-264. https://doi.org/10.1016/j.fsc.2016.03.004

Sabarinath, V. P., Thombare, P., Hazarey, P. V., Radhakrishnan, V., & Agrekar, S. (2010). Changes in maxillary alveolar morphology with nasoalveolar molding. *J Clin Pediatr Dent*, *35*(2), 207-212. https://doi.org/10.17796/jcpd.35.2.f80u21362566qr34

Saket, M., Saliminejad, K., Kamali, K., Moghadam, F. A., Anvar, N. E., & Khorram Khorshid, H. R. (2016). BMP2 and BMP4 variations and risk of non-syndromic cleft lip and palate. *Arch Oral Biol*, *72*, 134-137. https://doi.org/10.1016/j.archoralbio.2016.08.019

Sawardekar, K. P. (2005). Profile of major congenital malformations at Nizwa Hospital, Oman: 10-year review. *J Paediatr Child Health*, *41*(7), 323-330. https://doi.org/10.1111/j.1440-1754.2005.00625.x

Sekhon, P., Ethunandan, M., Markus, A., Krishnan, G., & Rao, C. B. (2011). Congenital anomalies associated with cleft lip and palate—an analysis of 1623 consecutive patients. *The Cleft Palate-Craniofacial Journal*, *48*(4), 371-378.

Shafi, T., Khan, M. R., & Atiq, M. (2003). Congenital heart disease and associated malformations in children with cleft lip and palate in Pakistan. *Br J Plast Surg*, *56*(2), 106-109. https://doi.org/10.1016/s0007-1226(03)00044-4

Shah, S. Y. A., RAHMAN, Z. A. A., Mirani, S. A., Shaikh, M. I., Khattak, M. N., & Sahito, M. A. (2015). Demographic data on the characterization of oral clefts in Malaysia. *Pakistan Oral & Dental Journal*, *35*(1).

Shkoukani, M. A., Chen, M., & Vong, A. (2013). Cleft lip–a comprehensive review. *Frontiers in pediatrics*, *1*, 53.

Shprintzen, R. J., Siegel-Sadewitz, V. L., Amato, J., & Goldberg, R. B. (1985). Anomalies associated with cleft lip, cleft palate, or both. *Am J Med Genet*, *20*(4), 585-595. https://doi.org/10.1002/ajmg.1320200404

Sischo, L., Clouston, S. A., Phillips, C., & Broder, H. L. (2016). Caregiver responses to early cleft palate care: A mixed method approach. *Health Psychol*, *35*(5), 474-482. https://doi.org/10.1037/hea0000262

Sitzman, T. J., Girotto, J. A., & Marcus, J. R. (2008). Current surgical practices in cleft care: unilateral cleft lip repair. *Plast Reconstr Surg*, *121*(5), 261e-270e. https://doi.org/10.1097/PRS.0b013e31816a9feb

Slaney, S. F., Oldridge, M., Hurst, J. A., Moriss-Kay, G. M., Hall, C. M., Poole, M. D., & Wilkie, A. O. (1996). Differential effects of FGFR2 mutations on syndactyly and cleft palate in Apert syndrome. *Am J Hum Genet*, *58*(5), 923-932.

Stanier, P., & Moore, G. E. (2004). Genetics of cleft lip and palate: syndromic genes contribute to the incidence of non-syndromic clefts. *Human Molecular Genetics*, *13*(suppl_1), R73-R81. https://doi.org/10.1093/hmg/ddh052

Stoll, C., Alembik, Y., Dott, B., & Roth, M. P. (2000). Associated malformations in cases with oral clefts. *Cleft Palate Craniofac J*, *37*(1), 41-47. https://doi.org/10.1597/1545-1569_2000_037_0041_amicwo_2.3.co_2

Subramanyam, D. (2020). An insight of the cleft lip and palate in pediatric dentistry-a review. *J Dent Oral Biol. 2020; 5 (2)*, *1164*.

Tan, T. Y., Kilpatrick, N., & Farlie, P. G. (2013). Developmental and genetic perspectives on Pierre Robin sequence. *Am J Med Genet C Semin Med Genet*, *163c*(4), 295-305. https://doi.org/10.1002/ajmg.c.31374

ten Dam, E., van der Heijden, P., Korsten-Meijer, A. G. W., Goorhuis-Brouwer, S. M., & van der Laan, B. F. A. M. (2013). Age of diagnosis and evaluation of consequences of submucous cleft palate. *International Journal of Pediatric Otorhinolaryngology*, *77*(6), 1019-1024. https://doi.org/https://doi.org/10.1016/j.ijporl.2013.03.036

Thong, M., Ho, J., & Khatijah, N. (2005). A population-based study of birth defects in Malaysia. *Annals of Human Biology*, *32*(2), 180-187.

van der Heijden, P., Dijkstra, P. U., Stellingsma, C., van der Laan, B. F., Korsten-Meijer, A. G. W., & Goorhuis-Brouwer, S. M. (2013). Limited evidence for the effect of presurgical nasoalveolar molding in unilateral cleft on nasal symmetry: a call for unified research. *Plast Reconstr Surg*, *131*(1), 62e-71e. https://doi.org/10.1097/PRS.0b013e318267d4a5

Vaziri Sani, F., Hallberg, K., Harfe, B. D., McMahon, A. P., Linde, A., & Gritli-Linde, A. (2005). Fate-mapping of the epithelial seam during palatal fusion rules out epithelial-mesenchymal transformation. *Dev Biol*, *285*(2), 490-495. https://doi.org/10.1016/j.ydbio.2005.07.027

Venkatesh, R. (2009). Syndromes and anomalies associated with cleft. *Indian Journal of Plastic Surgery*, *42*(S 01), S51-S55.

Verloes, A. (2005). Updated diagnostic criteria for CHARGE syndrome: a proposal. *Am J Med Genet A*, *133a*(3), 306-308. https://doi.org/10.1002/ajmg.a.30559

Vissers, L. E., van Ravenswaaij, C. M., Admiraal, R., Hurst, J. A., de Vries, B. B., Janssen, I. M., van der Vliet, W. A., Huys, E. H., de Jong, P. J., Hamel, B. C., Schoenmakers, E. F., Brunner, H. G., Veltman, J. A., & van Kessel, A. G. (2004). Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. *Nat Genet*, *36*(9), 955-957. https://doi.org/10.1038/ng1407

Vyas, T., Gupta, P., Kumar, S., Gupta, R., Gupta, T., & Singh, H. P. (2020). Cleft of lip and palate: A review. *Journal of family medicine and primary care*, *9*(6), 2621.

Walden, R. V., Taylor, S. C., Hansen, N. I., Poole, W. K., Stoll, B. J., Abuelo, D., & Vohr, B. R. (2007). Major congenital anomalies place extremely low birth weight infants at higher risk for poor growth and developmental outcomes. *Pediatrics*, *120*(6), e1512-1519. https://doi.org/10.1542/peds.2007-0354

Wallis, D. E., Roessler, E., Hehr, U., Nanni, L., Wiltshire, T., Richieri-Costa, A., Gillessen-Kaesbach, G., Zackai, E. H., Rommens, J., & Muenke, M. (1999). Mutations in the homeodomain of the human SIX3 gene cause holoprosencephaly. *Nat Genet*, *22*(2), 196-198. https://doi.org/10.1038/9718

Watkins, S. E., Meyer, R. E., Strauss, R. P., & Aylsworth, A. S. (2014). Classification, epidemiology, and genetics of orofacial clefts. *Clinics in plastic surgery*, *41*(2), 149-163.

Wilhelmsen, H. R., & Musgrave, R. H. (1966). Complications of cleft lip surgery. *Cleft Palate J*, *3*, 223-231.

Wilkie, A. O., Slaney, S. F., Oldridge, M., Poole, M. D., Ashworth, G. J., Hockley, A. D., Hayward, R. D., David, D. J., Pulleyn, L. J., Rutland, P., & et al. (1995). Apert syndrome results from localized mutations of FGFR2 and is allelic with Crouzon syndrome. *Nat Genet*, *9*(2), 165-172. https://doi.org/10.1038/ng0295-165

Wood, F. M. (1994). Hypoxia: another issue to consider when timing cleft repair. *Ann Plast Surg*, *32*(1), 15-18; discussion 19-20.

Worley, M. L., Patel, K. G., & Kilpatrick, L. A. (2018). Cleft Lip and Palate. *Clin Perinatol*, *45*(4), 661-678. https://doi.org/10.1016/j.clp.2018.07.006

Wyszynski, D. F., Sárközi, A., & Czeizel, A. E. (2006). Oral clefts with associated anomalies: methodological issues. *Cleft Palate Craniofac J*, *43*(1), 1-6. https://doi.org/10.1597/04-085r2.1

Xia, Y., Hu, B., Chen, J., Zheng, L., & Song, J. (2017). Association between the IRF6 rs2235371 polymorphism and the risk of nonsyndromic cleft lip with or without cleft palate in Chinese Han populations: A meta-analysis. *Arch Oral Biol*, *84*, 161-168. https://doi.org/10.1016/j.archoralbio.2017.09.032

Yi, N. N., Yeow, V. K., & Lee, S. T. (1999). Epidemiology of cleft lip and palate in Singapore--a 10-year hospital-based study. *Ann Acad Med Singap*, *28*(5), 655-659.

Zhang, Z., Fang, S., Zhang, Q., Chen, L., Liu, Y., Li, K., & Zhao, Y. (2014). Analysis of complications in primary cleft lips and palates surgery. *J Craniofac Surg*, *25*(3), 968-971. https://doi.org/10.1097/scs.0000000000000832

Zou, W., Greenblatt, M. B., Shim, J. H., Kant, S., Zhai, B., Lotinun, S., Brady, N., Hu, D. Z., Gygi, S. P., Baron, R., Davis, R. J., Jones, D., & Glimcher, L. H. (2011). MLK3 regulates bone development downstream of the faciogenital dysplasia protein FGD1 in mice. *J Clin Invest*, *121*(11), 4383-4392. https://doi.org/10.1172/jci59041

Zucchero, T. M., Cooper, M. E., Maher, B. S., Daack-Hirsch, S., Nepomuceno, B., Ribeiro, L., Caprau, D., Christensen, K., Suzuki, Y., Machida, J., Natsume, N., Yoshiura, K., Vieira, A. R., Orioli, I. M., Castilla, E. E., Moreno, L., Arcos-Burgos, M., Lidral, A. C., Field, L. L., . . . Murray, J. C. (2004). Interferon regulatory factor 6 (IRF6) gene variants and the risk of isolated cleft lip or palate. *N Engl J Med*, *351*(8), 769-780. https://doi.org/10.1056/NEJMoa032909