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Featured Review Article

# Treatment approaches to syndromes affecting craniofacial and dental structures

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ABSTRACT

*Background:* Patients with syndromes affecting the craniofacial and dental structures are treated mainly by an interdisciplinary team. The orthodontist is involved in the team since the child's birth. The objective of orthodontic treatment during the neonatal period is to align the maxillary alveolar segments, relieve the upper airway obstruction, or even facilitate feeding procedures. Further objectives are to normalize anatomical deviations and structural asymmetries, and guide the craniofacial growth in case of jaw discrepancies. Tooth shape/size anomalies or tooth agenesis problems should be carefully evaluated at the late mixed dentition stage. At the end of the craniofacial growth, orthognathic surgery may be considered for a better final aesthetic outcome.

*Methods:* Four syndromes with associated orofacial features in which the orthodontist is playing a pivotal role in the interdisciplinary management have been selected. Two of the syndromes involve orofacial clefts and two brachial arches and their prevalence is higher than 1 per 100,000 of the population.

*Results:* The syndromes are rare, and centralized care is required; many times, though, this is not feasible. Knowledge gaps on the etiopathogenesis, on gene and environmental interactions, on treatment modalities, and health effectiveness evaluation may complicate the therapeutic decision making. Continuity of care, consistency in the patient's record collection, and long-term follow-up could provide evidence for efficient treatment approaches, tailoring them to the patient's individual needs. Consideration of a patient's variation and the use of larger population data can assist in the application of precision medicine in larger groups or at a specific population level.

*Conclusions:* Early detection of syndromes affecting craniofacial and dental structures is vital for early identification of severe or life-threatening complications and patients' customized, integrated, long-term planning.



## 1. Introduction

Syndromes affecting the craniofacial and dental structures show a wide spectrum and may have a different degree of severity. These patients are mainly treated by an interdisciplinary team, which holds the potential for comprehensive services, reduced burden of care, and customized treatment modalities. Medical and dental specialists, including geneticists, pediatricians, plastic/maxillofacial surgeons, orthodontists, pediatric dentists, otolaryngologists, speech pathologists, and health care providers who have the clinical expertise are part of the team. The dental specialists are aiming to promote oral health, manage the structural and tooth size-shape abnormalities and craniofacial growth, and treat the malocclusions and craniofacial discrepancies. The orthodontic treatment involves the guidance of facial development since the first hours of the child's birth. Early diagnosis is of vital importance not only for the evaluation of prognostic factors and long-term planning, but also because these conditions can range from being very mild to severe and life-threatening. The fact is that not all children have access to the interdisciplinary teams because of the imbalance of centers' centralization and the geographic accessibility of the patients. Furthermore, the lack of sufficient scientific and medical knowledge impedes the establishment of optimal treatment modalities for these patients. Often treatment is based on parents' or patients' demands or priorities, and symptomatic and supportive treatment may be provided to meet the needs of the affected patients.

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**Table 1**
Syndromes involving oral clefts, synonyms, OMIM, Orpha, gene, genomic locations, inheritance pattern, and prevalence

| Syndrome | Synonyms | OMIM | Orpha | Gene | Locus | Inheritance | Prevalence/100,000 |
|---|---|---|---|---|---|---|---|
| Pierre Robin Sequence | Glossoptosis, micrognathia, and cleft palate<br>Pierre Robin malformation<br>Pierre Robin malformation sequence<br>Pierre Robin syndrome<br>Pierre Robin anomalad<br>Robin sequence<br>Robin syndrome | 261800 | 718 | *SOX9* | 17q24.3-q25.1 | New mutation (autosomal dominant) | 7.1–11.8 |
| EEC 1 | Ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome | 129900 | 1896 | — | 7q11.2-q21.3 | Autosomal dominant | <0.1 |
| EEC 3 | | 604292 | 2440 | *TP63* | 3q28 | Autosomal dominant<br>New mutations | 5.4 |

OMIM, Online Mendelian Inheritance in Man.

The primary goal of this article is to present an overview of diagnostic craniofacial and dental features and a comprehensive treatment approach for the orthodontist that is involved in the treatment of patients with syndromes affecting the craniofacial and dental structure. Furthermore, to promote communication among the interdisciplinary team members for long-term, customized, and integraded treatment of these patients.

## 2. Methods

For this review, four syndromes have been selected according to the following criteria:

1. Existing supportive literature documentation for the presence of associated facial, oral, and/or dental features.
2. The prevalence of the disorders is higher than 1 per 100,000 of the population.

The following two categories of syndromes are presented:

1. Syndromes involving orofacial clefts
2. Syndromes involving branchial arches

Information is provided on the possible etiopathogenic mechanism; general, craniofacial, and dental features; and treatment approaches. Synonyms, Online Mendelian Inheritance in Man (OMIM), Orpha, gene, genomic location, inheritance pattern, and prevalence are presented in Tables 1 and 2.

## 3. Results

### 3.1. Syndromes involving orofacial clefts

The syndromes presented in this category are Pierre Robin Sequence (PRS) and ectrodactyly-ectodermal dysplasia-clefting syndrome (EEC-S). Cleft lip and/or cleft palate (CL/P) diagnostic features and treatment considerations are presented additionally to the features and the treatment modalities of PRS and EEC-S.

#### 3.1.1. General

CL/P is the most common orofacial deformity. The overall incidence of orofacial clefts (OFCs) ranges from 1.7 per 1000 live births, but it varies depending on socioeconomic conditions, ethnicity, and geographic background [1]. Even though almost 70% of the OFCs are nonsyndromic, more than 500 syndromes are associated with CL/P [2]. Certain types of OFCs are associated more often with a syndrome, such as the isolated cleft lip and palate. In almost 50% of these patients, an identified syndrome has been reported. This can be explained because there is a genetic and embryologic distinction among the clefts on the lip and primary palate and those on the secondary palate [2]. However, genetic and environmental triggers that contribute to the pathogenesis of syndromic clefts also can be related to nonsyndromic clefts [3].

#### 3.1.2. Craniofacial features

The surgical procedures have an impact on craniofacial growth. Evaluation of patients with unoperated clefts has shown that these patients have normal craniofacial growth potential. Palatal scaring is the reason for maxillofacial growth impairment, which depends on the techniques addressed or the surgeon's skills, and not on the timing of the surgical procedures [4].

#### 3.1.3. Oral and dental features

There is co-occurrence of tooth agenesis (TA) and OFCs not only inside but also outside the cleft region, indicating the common underlining genetic mechanism. The most commonly missing teeth besides the lateral incisors in the cleft region are the maxillary and mandibular second premolars [5]. TA prevalence of patients with CL/P is more than 50%. The agenesis of the lateral incisor on the cleft side could be the result of tissue insufficiency during

**Table 2**
Syndromes involving branchial arches, synonyms, OMIM, Orpha, gene, genomic locations, inheritance pattern, and prevalence

| Syndrome | Synonyms | OMIM | Orpha | Gene | Locus | Inheritance | Prevalence/100,000 |
|---|---|---|---|---|---|---|---|
| Craniofacial microsomia | Hemifacial microsomia<br>Goldenhar syndrome<br>Oculoauroventriculovertebral spectrum<br>Oculoauroventriculovertebral dysplasia<br>Facio-auriculo-vertebral sequence | 164210 | 374 | Heterogeneous | 14q32 and others | Mainly sporadic, some autosomal dominant | 1.8–3.9 |
| Treacher-Collins 1 | Treacher-Collins syndrome<br>Treacher-Collins-Francetti syndrome<br>Mandibulafacial dysostosis | 154500 | 861 | *TCOF1* | 5q32 | Autosomal dominant | 2.0 |
| Treacher-Collins 2 | — | 613717 | 861 | *POLR1D* | 13q12 | Autosomal dominant | |
| Treacher-Collins 3 | Mandibulofacial dysostosis, Treacher-Collins type (autosomal recessive) | 248390 | 861 | *POLR1C* | 6p21 | Autosomal recessive | |

OMIM, Online Mendelian Inheritance in Man.

embryogenesis. Peg-shaped, ectopic eruption of the maxillary permanent molars, and the infraocclusion of primary molars, are among the most common dental findings reported [6]. Patients with CL/P treated with a multiband appliance have a higher incidence of apical root resorption on the teeth located in the vicinity of the cleft. This can be attributed to the special anatomic characteristics of the bone and the morphological variations of the teeth located in the cleft [7].

#### 3.1.4. Treatment

Nowadays, both two-dimensional (2D) and 3D sonography between 18 and 24 weeks of gestation give a reliable diagnosis, especially in the high-risk population. Psychological support and counseling on treatment management is provided to both parents at this time. Infant orthopedics have been critically evaluated, and they are used only from half of the European cleft teams [1]. Nasolabial molding has been introduced for reshaping the alveolar segments, the nasal cartilage, and the columella [8]. Not enough evidence, though, supports these benefits. Different surgical procedures and almost as many different protocols as the European cleft centers have been described [1]. The vast majority of the European centers (71%) follow a two-step closing procedure of the cleft, first the lip at 2 to 6 months, followed by the soft and hard palate closure at approximately the first year of life [1].

Speech hypernasality and proper articulation have to be addressed before the child goes to grade school. At the early mixed dentition stage, orthodontic considerations are the crossbite correction, the tooth eruption guidance, and the treatment of the sagittal maxillary deficiency with a face mask. The secondary bone grafting procedure is performed before the eruption of the permanent canines (8–11 years), and typically after the maxillary expansion. The goal is to ascertain the arch symmetry and the periodontal health on the cleft side. The grafted bone becomes radiographically indistinguishable after approximately 3 months. The orthodontic tooth movement with a multiband appliance, on the cleft side, can then start actively again [7]. Maxillary distraction osteogenesis for the management of a wide defect in the cleft area has been reported [9]. The missing or often severe hypoplastic lateral incisors will be replaced by dental implants, taking into consideration the smile esthetics and the growth potential of the patients. Often orthodontic space opening is required, to facilitate proper placement of implants. Orthodontic space closure, though, is the selected treatment for a better aesthetic outcome and the maintenance of healthy periodontal structures. The patient's skeletal classification is also considered for space management in the cleft area. Bone anchorage devices are used in patients with multiple TA for maxillary expansion or space closure when the anchorage control is compromised. Cone-beam computed tomography (CT) technology is a valuable tool for the diagnosis and treatment planning of these patients for the evaluation of the quality and quantity of the bone, airway volume, the anatomy of the temporomandibular joint, root resorption, and so forth.

### 3.2. Pierre Robin sequence

#### 3.2.1. General

Pierre Robin (PR) syndrome was the first term used, although now called Pierre Robin Sequence (PRS) because a sequential chain of malformations is involved [10]. Micrognathia and glossoptosis, which leads secondarily to upper airway obstruction (UAO), are the cardinal characteristics of this condition. Obstructive sleep apnea (OSA) in different degrees of severity occurs in 50% to 100% of individuals with PRS. The hypoplastic mandible can be diagnosed before birth with the help of ultrasonography. CL/P is observed in almost 75% to 100% of the patients [11].

Almost 60% of the PRS may occur associated with a syndrome (sPRS). The most common associated syndromes are 22q11.2 deletion and Stickler syndrome, followed by van der Woude, Möbius, or Treacher Collins Syndrome (TCS). Most isolated PRS arise through de novo mutations. In the rarer familial cases of isolated PRS (nsPRS) (10%), the mode of inheritance is mainly autosomal dominant (AD), although the genetic mechanism has not yet been elucidated. PRS has been associated with a mutation in the *SOX9* gene, as it is related to embryonic mandibular hypoplasia.

#### 3.2.2. Craniofacial features

Newborns with PRS (age at CT: 33 days) were compared with unaffected individuals and showed reduced mandibular volume, ramus, and body length. After treatment with mandibular distraction osteogenesis (MDO) at 4 months of age, the patients with PRS had mandibular rami shorter and mandibular bodies longer in comparison with the controls [12]. In lateral cephalometric measurements, the ratio between ramus height and mandibular body is higher, as also is the gonial angle and the inclination of the palatal and mandibular planes in comparison with the unaffected controls [13]. The short mandibles (micrognathia) of the patients with PRS showed no catch-up growth during adolescence [14,15]. However, in a survey in which 101 European centers participated, catch-up growth was reported in almost three-quarters of the participating clinicians [16]. There are diagnoses and management inconsistencies in the presented data.

The morphology of the mandible of individuals with sPRS has a poorer outcome in comparison with individuals with nsPRS [17]. Microcephaly or macrocephaly, facial dysmorphic features, and hypoplasia of zygomatic bones [18] may be attributed to the generalized growth impairment.

#### 3.2.3. Oral and dental features

The dorsal abnormal position of the tongue (glossoptosis), can result in respiratory obstruction, vagal syncope, and feeding problems. Ankyloglossia is observed in almost 13% of patients with PRS [19]. TA of patients with PRS, in the mandible only, ranges up to 50% (excluding the third molars). The most commonly affected teeth are the second mandibular premolars [20]. The primary and secondary operations affected the maxillary arch development of the nsPRS group significantly in comparison with the isolated cleft lip and palate group, and these findings were consistent until the end of the growth [21]. This also can be attributed to poor neuromuscular development and intrinsic growth factors [22].

#### 3.2.4. Treatment

The treatment for children with PRS should address respiratory distress, feeding difficulties, and the treatment of severe mandibular micrognathia. Management of PRS, especially when associated with other syndromes, is challenging. However, there is no consensus on specific management strategies for these patients [23].

Prone and lateral positioning, nasopharyngeal airway, and continuous positive airway pressure are nonsurgical interventions that can be effective in mild forms of PRS. The tongue-lip adhesion and the tongue-mandibular adhesion are short-term solutions for mild forms of UAO with potential complications on the tongue (laceration or ankyloglossia) and salivary glands [24]. The preepiglottic baton-plate was effective for the treatment of UAO in a cohort of patients with PRS [25]. Almost 1 of 4 patients between the ages of 1 and 18 years have respiratory problems [26]. Concerns have been raised about the effect of conservative treatment interventions of UAO on the growth and neurological development of these children.

MDO is effective and provides a quick solution in respiratory distress in selected patients, preventing tracheostomy [27]. Scar tissue and damage of developing teeth are the iatrogenic consequences related to MDO [24].

### 3.3. Ectrodactyly-ectodermal dysplasia-clefting syndrome

#### 3.3.1. General

EEC-S is an AD disorder resulting from a missense mutation in the *TP63* gene, with a variable clinical phenotype and degree of penetrance. It is characterized by three cardinal signs: ectrodactyly ("claw-like" hands and feet), ectodermal dysplasia (ED), and OFC. ED often leads to skin hypopigmentation, dry skin, hyperkeratosis, or skin atrophy, nail dystrophy, fine and sparse hair and eyebrows, and reduced or absence of salivary and sweat glands. Other features of this syndrome include lacrimal duct atresia and dry eye, urogenital abnormalities, mammary gland/nipple hypoplasia, hearing loss [28], cardiomegaly [29] or Tetralogy of Fallot. In addition, hypothalamo-pituitary dysfunction together with growth retardation [30] have also been reported.

#### 3.3.2. Craniofacial features

CL/P is among the cardinal signs of the syndrome, observed in 40% to 70% of the patients with EEC and mostly are bilaterally affected [28]. Only 1% to 5% of the patients with EEC have midfacial, zygomatic, maxillary, and mandibular hypoplasia, microcephaly, and premaxillary protrusion [30].

#### 3.3.3. Oral and dental features

Patients with EEC have the primary and permanent dentitions affected [31]. Dental anomalies have been reported, including enamel and root structural defects [32] and tooth shape-size deviations (peg-shaped and generalized microdontia) [33]. TA varies from a mild form to complete anodontia [33]. The dental age and tooth eruption are delayed [31]. The prevalence of dental caries is increased, and oral hygiene is poor, most probably due to the hand-grasping impairment. Protruding upper lip [28], thin raphe of the filtrum and congenital indentation of the upper lip vermillion, dry mouth and oral mucosa hypertrophy, oral candidiasis [34], and chronic ulcerative stomatitis [35], often associated with deep tongue fissures [34], are the most common oral findings described in isolated cases.

#### 3.3.4. Treatment

Symptomatic management from a multidisciplinary team to solve functional disabilities is required. Hypodontia and maxillary hypoplasia make orthodontic treatment challenging. In case of hypodontia, the primary teeth should be preserved as long as possible, or tooth autotransplantation should be considered for the maintenance of the volume of the alveolar bone. A partial denture is often mandatory from childhood, followed by extensive prosthodontic rehabilitation after growth cessation. Orthodontic treatment, in combination with Le Fort I osteotomy or maxillary distraction osteogenesis, is advocated for the correction of the maxillary hypoplasia.

### 3.4. Syndromes involving branchial arches

Branchial arch syndromes affect the first and second branchial arch derivatives and alter facial appearance and function, compromising facial movement, airway, feeding, and hearing. Craniofacial microsomia (CM) and TCS are the most frequent syndromes in this group.

### 3.5. CM (hemifacial microsomia)

#### 3.5.1. General

CM is the second most common craniofacial condition after CL/P. Recently, the term CM has been selected to replace the term "hemifacial macrosomia" [36] and describes a broad phenotypic spectrum of unilateral or bilateral underdevelopment of craniofacial structures [37].

The aliases of CM are the Goldenhar syndrome, oculo-auriculo-vertebral (OAV) dysplasia, OAV spectrum (OAVS), and facio-auriculo-vertebral sequence. The pathogenesis of CM is unclear and multifactorial [38]. The pathogenic mechanism maybe is related to vascular abnormality close to the Meckel's cartilage, resulting in disruption of the chondrogenesis [38]. Although AD inheritance has been described in a family with OAVS, the sporadic cases reported and discordances in monozygotic twins, implicate the pathogenesis. Maternal diabetes [39] or exposure to teratogens can result in these phenotypes. By prenatal ultrasonography at the 24th gestational week, marked anatomical asymmetries can be identified.

#### 3.5.2. Craniofacial features

A 3D analysis of the deformed mandible showed that due to the mandibular remodeling process, the defect could not be limited only to the one side. The mandible is rotated toward the affected side, and compensatory remodeling on the unaffected side will take place. The main anatomic deviations are observed in the condyle, the mandibular angle, and the body in a descending order [40], followed by secondary deformation of the maxilla, nose, and orbit.

As the patient grows, the skeletal and soft tissue deformity is progressive, in certain cases, although is associated with facial nerve palsy deteriorating the facial asymmetry [40].

Uni- or bilateral ear abnormalities associated with hearing impairment have been reported in almost 90% [41] of the affected patients. Cephalometric analysis showed a retrognathic mandible, a convex facial profile, and a steep gonial angle [42]. The smaller mandibular body and ramus at the affected side were associated with an inclination of the occlusal plane. Nevertheless, the affected mandibular side had a growth rate similar to a control nonaffected population [43]. In a 3D-imaging evaluation, there was no growth modification in patients with absence or severe deformity of the ramus [44]. Thus, the growth impairment is varying according to the deformity of the condylar cartilage. Almost 10% of patients with CM are associated with CL/P. A multicenter cohort of 755 patients with CM showed that patients with bilateral involvement had a more severe phenotype [45]. Mandibular canal variations, especially in the most severe cases, should be carefully evaluated before surgical interventions.

#### 3.5.3. Oral and dental features

The prevalence of TA is approximately 25%, and the most affected teeth are the mandibular second premolars and second molars [46]. Tooth development is delayed in patients with CM, but asymmetric tooth development between the affected and nonaffected side has been observed only in the most severe cases [46]. Patients with CM have often mild tongue deformities.

#### 3.5.4. Treatment

The identification of the etiopathogenic area [44] and differentiation of the CM from conditions related to trauma, local infection, or iatrogenic factors are of importance for treatment planning. Different classification systems, aiming to facilitate the mutual understanding among clinicians, have been described (OMENS, SAT, Pruzansky, and the Pruzansky modification by Kaban). These systems are based on 2D imaging and are rather accurate when the

ramus and mandibular body are involved and poor when the head of the condyle and the glenoid fossa are implicated [44].

No "catch-up" growth occurs on the affected side. Recent studies, though, in 3D reconstructed images, showed that mainly the condyle and less the mandibular body, ameliorate with age only in less severe cases [44]. Treatment involves orthodontic and surgical interventions for the correction of facial asymmetry. Orthopedic treatment with a hybrid functional appliance (Frankel type I) [47] aims to correct the overall facial symmetry and growth by normalizing the mandibular position and stretching the deficient soft tissue and muscles.

MDO treatment in primary and early mixed dentitions was associated with long-term relapse. Contrarily, patients treated in the late mixed dentition demonstrated more stable results 4 years post-distraction [48].

The timing of surgical intervention is still controversial. In the mild expression of CM, MDO, or osteotomies without bone grafts are adequate to improve facial asymmetry. In more severe types though, ramus/condyle or even temporomandibular joint construction are performed. In cases of neurological involvement, physiotherapy may assist facial expression after the orthognathic surgery [49].

### 3.6. Treacher Collins syndrome

#### 3.6.1. General

TCS is an AD condition with a high degree of penetrance and variable expressivity. Nevertheless, more than 60% of cases reported are de novo mutations.

Three types of this condition have been described. In most cases, the mutation is in the gene *TCOF1*, which is essential for normal cell function and the neural crest specification [50].

Antioxidants as dietary supplements have been *proposed* as preventive agents during pregnancy against oxidative stress, which is related to DNA distortion in conditions such as TCS [51].

These patients have normal cognitive development but rather lower height and weight in comparison with their peers [52].

Associated malformations may involve most commonly the heart (12%), whereas the brain, the kidney, and the limb are considered rather rare [52].

#### 3.6.2. Craniofacial features

Maxillary hypoplasia and mandibular retrognathism have been described in all types of TCS [52]. The cardinal characteristic of 70 patients with TCS1 was the downward-slanting palpebral fissures (in 100% of the patients), malar hypoplasia (99%), conductive deafness (91%), followed by mandibular hypoplasia (87%), atresia of external ear canal (72%), microtia (71%), coloboma of the lower eyelid (65%), facial asymmetry (53%) [53], CL/P (22%), and choanal stenosis or atresia (14%) [53]. The absence of the zygomatic arch and cleft palate (28%) have been reported mainly in the most severe cases. The "antegonial notching" is deep, resembling that of patients with condylar hypoactivity or condylar growth arrest [52]. Anterior open bite, restricted mouth opening, and complex temporomandibular joint abnormalities also have been reported [52].

Additional deviations of the shape of the neurocranium have been described, such as diminished bitemporal width, anterior-posterior length, and cranial base [52]. A classification system, for the mandible of patients with TCS, has been presented, based on the severity of condylar hypoplasia, mandibular retrognathia and the angulation of the mandibular plane (condylion-gonion-menton angle) [54]. Mandibular clockwise rotation was observed in a group of children followed from 3 to 22 years of age [55]. In a prospective study evaluation, all but one (18/19) of the patients with TCS were diagnosed with OSA. OSA is usually severe and present in all ages.

#### 3.6.3. Oral and dental features

Children with TCS children have severe malocclusions, and almost 60% of the affected children have dental anomalies. TA is the most frequent anomaly, and the most affected teeth are the mandibular second premolars, followed by maxillary second premolars, lateral incisors, and maxillary canines [56]. Enamel hypoplasia and high caries risk linked to mouth breathing, poor salivary gland secretion, dental crowding, and soft diet, due to mastication problems, have been reported. Also, impacted, malpositioned, and supernumerary maxillary teeth are among the common dental anomalies [56].

#### 3.6.4. Treatment

Patients with TCS need team coordination for treatment of the OSA, speech disorders, feeding and swallowing difficulties, ear infections or hearing and vision impairment, and many other problems. The treatment, in newborn patients, is prioritized to respiratory distress and feeding difficulties, and in the period of the first 3 months after birth to hearing, vision, and articulation problems [57]. The orthodontic/orthognathic treatment of patients with TCS focuses on correction of the maxillary constriction and mandibular retrognathism, open bite and overjet, crowding, and the establishment of proper function and aesthetics. Orthognathic correction often requires Le Fort I and bilateral sagittal split osteotomies and, many times, genioplasty. The zygomatic area can be reconstructed with onlay bone grafts or vascularized bone flap procedures [57] from calvarial bone, rib cartilage, or implants.

## 4. Discussion

This article presented an update on clinical phenotypes and treatment modalities of syndromes affecting the craniofacial and dental structures. Knowledge gaps and differences in definitions, documentation, and management of these patients demand the collaboration of different disciplines on a national or international basis [16], including patients' and parents' satisfaction and their psychological concerns.

Health care models should integrate precision medicine, focusing on individual-level variation for personalized prevention and treatment through clinical pharmacogenomics, and genetic counseling for efficient and safe delivery of care. Protection against teratogenic agents from early pregnancy and implementation of antioxidants [51], and other agents that may ameliorate or even prevent the pathogenesis of these conditions need further research investigations [38]. Deep phenotyping and 3D facial imaging applications can contribute to a mechanistic diagnosis of patients with craniofacial anomalies.

Further data on facial phenotyping may unravel the facial phenotype/genotype correlations. As such is the small philtrum width phenotype of the upper lip, which is associated with the genetic risk of nonsyndromic clefts among the nonaffected individuals [58]. Genome-wide association studies, capturing the dynamic facial movement, can explore neurological and morphological facial characteristics [58], identifying conditions with neurological involvement. The 3D stereophotogrammetry is a valuable tool for precise facial growth evaluation in children with facial deformities. The evolution of 3D technology offers a precise diagnosis and treatment planning to the orthognathic and reconstructive surgery. The 3D printing technology provides an easy and quick fabrication of the infant orthopedic appliance and customized prosthesis for facial reconstruction [59].

## 5. Conclusions

- Early diagnosis of syndromes affecting craniofacial and dental structures is essential for immediate identification of life-threatening complications like UAO and early interventions and planning of orthopedic/orthodontic craniofacial growth modification.
- Personalized, long-term, integrated treatment care should be advocated, with concern on patients' needs.
- Deep phenotyping of craniofacial and dental structures is needed for the identification of genetic variants and environmental factors in the pathogenesis of these syndromes.

## References


[1] Mossey PA, Little J, Munger RG, Dixon MJ, Shaw WC. Cleft lip and palate. Lancet 2009;374:1773–85.
[2] Dixon MJ, Marazita ML, Beaty TH, Murray JC. Cleft lip and palate: understanding genetic and environmental influences. Nat Rev Genet 2011;12:167–78.
[3] Wang Y, Sun Y, Huang Y, et al. Association study between Van der Woude Syndrome causative gene GRHL3 and nonsyndromic cleft lip with or without cleft palate in a Chinese cohort. Gene 2016;588:69–73.
[4] Bartzela T, Katsaros C, Ronning E, et al. A longitudinal three-center study of craniofacial morphology at 6 and 12 years of age in patients with complete bilateral cleft lip and palate. Clin Oral Investig 2012;16:1313–24.
[5] Bartzela TN, Carels CE, Bronkhorst EM, Kuijpers-Jagtman AM. Tooth agenesis patterns in unilateral cleft lip and palate in humans. Arch Oral Biol 2013;58:596–602.
[6] Rizell S, Bellardie H, Karsten A, et al. Scandcleft randomized trials of primary surgery for unilateral cleft lip and palate: dental anomalies in 8-year olds [published online ahead of print October 3, 2019]. *Eur J Orthod*, https://doi.org/10.1093/ejo/cjz070.
[7] Bartzela TN, Mang de la Rosa MR, Wolf K, Schmidt A, Opitz C. Apical root resorption after orthodontic treatment in patients with unilateral cleft lip and palate [published online ahead of print August 13, 2019]. *Clin Oral Investig*, https://doi.org/10.1007/s00784-019-03044-2.
[8] Grayson BH, Cutting CB. Presurgical nasoalveolar orthopedic molding in primary correction of the nose, lip, and alveolus of infants born with unilateral and bilateral clefts. Cleft Palate Craniofac J 2001;38:193–8.
[9] Zhang J, Zhang W, Shen SG. Segmental maxillary distraction osteogenesis with a hybrid-type distractor in the management of wide alveolar cleft [published online ahead of print January 1, 2018]. *Cleft Palate Craniofac J*, https://doi.org/10.1177/1055665618763329.
[10] Gangopadhyay N, Mendonca DA, Woo AS. Pierre robin sequence. Semin Plast Surg 2012;26:76–82.
[11] van Lieshout MJ, Joosten KF, Hoeve HL, Mathijssen IM, Koudstaal MJ, Wolvius EB. Unravelling Robin sequence: considerations of diagnosis and treatment. Laryngoscope 2014;124:E203–9.
[12] Zellner EG, Reid RR, Steinbacher DM. The Pierre Robin mandible is hypoplastic and morphologically abnormal. J Craniofac Surg 2017;28:1946–9.
[13] Suri S, Ross RB, Tompson BD. Craniofacial morphology and adolescent facial growth in Pierre Robin sequence. Am J Orthod Dentofacial Orthop 2010;137:763–74.
[14] Daskalogiannakis J, Ross RB, Tompson BD. The mandibular catch-up growth controversy in Pierre Robin sequence. Am J Orthod Dentofacial Orthop 2001;120:280–5.
[15] Ozawa TO, Lorenzoni DC, de Oliveira LG, da Silva Filho OG. Facial profile evaluation of isolated Pierre Robin sequence. Cleft Palate Craniofac J 2012;49:546–52.
[16] van Lieshout MJ, Joosten KF, Mathijssen IM, et al. Robin sequence: a European survey on current practice patterns. J Craniomaxillofac Surg 2015;43:1626–31.
[17] Rogers GF, Lim AA, Mulliken JB, Padwa BL. Effect of a syndromic diagnosis on mandibular size and sagittal position in Robin sequence. J Oral Maxillofac Surg 2009;67:2323–31.
[18] Gomez-Ospina N, Bernstein JA. 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 2016;170A:870–80.
[19] Butow KW, Hoogendijk CF, Zwahlen RA. Pierre Robin sequence: appearances and 25 years of experience with an innovative treatment protocol. J Pediatr Surg 2009;44:2112–8.
[20] Antonarakis GS, Suri S. Prevalence and patterns of permanent tooth agenesis in patients with nonsyndromic Pierre Robin sequence. Am J Orthod Dentofacial Orthop 2014;145:452–60.
[21] Laitinen SH, Ranta R. Sizes of dental arches in young adult patients with Pierre Robin sequence and isolated cleft palate. Acta Odontol Scand 1998;56:85–9.
[22] Sher AE. Mechanisms of airway obstruction in Robin sequence: implications for treatment. Cleft Palate Craniofac J 1992;29:224–31.
[23] van Lieshout MJ, Joosten KF, Mathijssen IM, Koudstaal MJ, Wolvius EB, van der Schroeff MP. Non-surgical and surgical interventions for airway obstruction in children with Robin Sequence. J Craniomaxillofac Surg 2016;44:1871–9.
[24] Butow KW, Naidoo S, Zwahlen RA, Morkel JA. Pierre Robin sequence: subdivision, data, theories, and treatment–Part 4: Recommended management and treatment of Pierre Robin sequence and its application. Ann Maxillofac Surg 2016;6:44–9.
[25] Buchenau W, Wenzel S, Bacher M, Muller-Hagedorn S, Arand J, Poets CF. Functional treatment of airway obstruction and feeding problems in infants with Robin sequence. Arch Dis Child Fetal Neonatal Ed 2017;102:F142–6.
[26] van Lieshout MJS, Joosten KFM, Koudstaal MJ, et al. Management and outcomes of obstructive sleep apnea in children with Robin sequence, a cross-sectional study. Clin Oral Investig 2017;21:1971–8.
[27] Ren XC, Gao ZW, Li YF, Liu Y, Ye B, Zhu SS. The effects of clinical factors on airway outcomes of mandibular distraction osteogenesis in children with Pierre Robin sequence. Int J Oral Maxillofac Surg 2017;46:805–10.
[28] Wojcicki P, Wysocki M, Wojcicka K. Ectrodactyly-ectodermal dysplasia-clefting syndrome-plastic surgeon's considerations. J Craniofac Surg 2010;21:1388–92.
[29] Miner ME, Rea GL, Handel S, Bertz J. Trigeminal neuralgia due to dolichoectasia: angiographic and CT findings in a patient with the EEC syndrome. Neuroradiology 1980;20:163–6.
[30] Roelfsema NM, Cobben JM. The EEC syndrome: a literature study. Clin Dysmorphol 1996;5:115–27.
[31] Klein OD, Oberoi S, Huysseune A, Hovorakova M, Peterka M, Peterkova R. Developmental disorders of the dentition: an update. Am J Med Genet C Semin Med Genet 2013;163c:318–32.
[32] Vernersson Lindahl E, Garcia EL, Mills AA. An allelic series of Trp63 mutations defines TAp63 as a modifier of EEC syndrome. Am J Med Genet 2013;161A:1961–71.
[33] waWallis CE. Ectrodactyly (split-hand/split-foot) and ectodermal dysplasia with normal lip and palate in a four-generation kindred. Clin Genet 1988;34:252–7.
[34] King NM, Tong MC, Ling JY. The ectrodactyly-ectodermal dysplasia-clefting syndrome: a literature review and case report. Quintessence Int 1994;25:731–6.
[35] Romano RA, Solomon LW, Sinha S. Tp63 in oral development, neoplasia, and autoimmunity. J Dent Res 2012;91:125–32.
[36] Birgfeld C, Heike C. Craniofacial microsomia. Clin Plast Surg 2019;46:207–21.
[37] Renkema RW, Caron C, Pauws E, et al. Extracraniofacial anomalies in craniofacial microsomia: retrospective analysis of 991 patients. Int J Oral Maxillofac Surg 2019;48:1169–76.
[38] Chen Q, Zhao Y, Shen G, Dai J. Etiology and pathogenesis of hemifacial microsomia. J Dent Res 2018;97:1297–305.
[39] Guida V, Sinibaldi L, Pagnoni M, et al. A de novo proximal 3q29 chromosome microduplication in a patient with oculo auriculo vertebral spectrum. Am J Med Genet 2015;167a:797–801.
[40] Choi J, Park SW, Kwon GY, et al. Influence of congenital facial nerve palsy on craniofacial growth in craniofacial microsomia. J Plast Reconstr Aesthet Surg 2014;67:1488–95.
[41] Beleza-Meireles A, Hart R, Clayton-Smith J, et al. Oculo-auriculo-vertebral spectrum: clinical and molecular analysis of 51 patients. Eur J Med Genet 2015;58:455–65.
[42] Ongkosuwito EM, van Neck JW, Wattel E, van Adrichem LN, Kuijpers-Jagtman AM. Craniofacial morphology in unilateral hemifacial microsomia. Br J Oral Maxillofac Surg 2013;51:902–7.
[43] Ongkosuwito EM, van Vooren J, van Neck JW, et al. Changes of mandibular ramal height, during growth in unilateral hemifacial microsomia patients and unaffected controls. J Craniomaxillofac Surg 2013;41:92–7.
[44] Kim BC, Bertin H, Kim HJ, et al. Structural comparison of hemifacial microsomia mandible in different age groups by three-dimensional skeletal unit analysis. J Craniomaxillofac Surg 2018;46:1875–82.
[45] Caron C, Pluijmers BI, Wolvius EB, et al. Craniofacial and extracraniofacial anomalies in craniofacial microsomia: a multicenter study of 755 patients. J Craniomaxillofac Surg 2017;45:1302–10.
[46] Ongkosuwito EM, de Gijt P, Wattel E, Carels CE, Kuijpers-Jagtman AM. Dental development in hemifacial microsomia. J Dent Res 2010;89:1368–72.
[47] Cassi D, Magnifico M, Gandolfinini M, Kasa I, Mauro G, Di Blasio A. Early orthopaedic treatment of hemifacial microsomia. Case Rep Dent 2017;2017:7318715.
[48] Lu TC, Kang GC, Yao CF, et al. Simultaneous maxillo-mandibular distraction in early adolescence as a single treatment modality for durable correction of type II unilateral hemifacial microsomia: follow-up till completion of growth. J Craniomaxillofac Surg 2016;44:1201–8.
[49] Magnifico M, Cassi D, Kasa I, Di Blasio M, Di Blasio A, Gandolfini M. Pre- and postsurgical orthodontics in patients with Moebius syndrome. Case Rep Dent 2017;2017:1484065.
[50] Hayano T, Yanagida M, Yamauchi Y, Shinkawa T, Isobe T, Takahashi N. Proteomic analysis of human Nop56p-associated pre-ribosomal ribonucleoprotein complexes. Possible link between Nop56p and the nucleolar protein treacle responsible for Treacher Collins syndrome. J Biol Chem 2003;278:34309–19.
[51] Sakai D, Dixon J, Achilleos A, Dixon M, Trainor PA. Prevention of Treacher Collins syndrome craniofacial anomalies in mouse models via maternal antioxidant supplementation. Nat Commun 2016;7:10328.

[52] Posnick JC, Ruiz RK. Treacher Collins syndrome: current evaluation, treatment, and future directions. Cleft Palate Craniofac J 2000;37:434.
[53] Vincent M, Genevieve D, Ostertag A, et al. Treacher Collins syndrome: a clinical and molecular study based on a large series of patients. Genet Med 2016;18:49–56.
[54] Ligh CA, Swanson J, Yu JW, Samra F, Bartlett SP, Taylor JA. A morphological classification scheme for the mandibular hypoplasia in Treacher Collins syndrome. J Craniofac Surg 2017;28:683–7.
[55] Arvystas M, Shprintzen RJ. Craniofacial morphology in Treacher Collins syndrome. Cleft Palate Craniofac J 1991;28:226–30. discussion 230–1.
[56] da Silva Dalben G, Costa B, Gomide MR. Prevalence of dental anomalies, ectopic eruption and associated oral malformations in subjects with Treacher Collins syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;101:588–92.
[57] Thompson JT, Anderson PJ, David DJ. Treacher Collins syndrome: protocol management from birth to maturity. J Craniofac Surg 2009;20:2028–35.
[58] Richmond S, Howe LJ, Lewis S, Stergiakouli E, Zhurov A. Facial genetics: a brief overview. Front Genet 2018;9:462.
[59] Day KM, Gabrick KS, Sargent LA. Applications of computer technology in complex craniofacial reconstruction. Plast Reconstr Surg Glob Open 2018;6:e1655.