Biological Basis of Branchial Arch Diseases

10

Ulrich Meyer

10.1 Introduction

Because tissue and organ structures of the head and neck migrate during fetal development, an understanding of embryologic development helps determine the origin and nature of congenital lesions [1]. Disorders of the frontonasal prominence (FNP) and the first and second branchial arches (BAs) are generally thought to result from a combination of inadequate migration and formation of facial tissues. Branchial arch disease is the term [2, 3] that describes the pathogenetic basis of a specific subset of craniofacial anomalies, also termed facial dysostoses, which can be subdivided into mandibulofacial dysostosis, which present with craniofacial defects only, and acrofacial dysostosis, which encompasses both craniofacial and limb anomalies. Knowledge of the genetic basis of human disease and its effect on embryologic development has greatly expanded in recent years. These malformations have etiologic and pathogenic similarities, specifically their unique deficiencies in global processes including ribosome biogenesis, DNA damage repair, and pre-mRNA splicing, all of which affect neural crest cell development and result in similar tissue-specific defects.

U. Meyer (✉)
Craniofacial Center, Kieferklinik Münster, Münster, Germany

University of Düsseldorf, Westdeutsche Kieferklinik, Moorenstrasse, Düsseldorf, Germany
e-mail: info@kieferklinik-muenster.de

10.2 Pathogenesis of Facial Development

Head and face development begins during early embryogenesis with formation of the frontonasal prominence and the pharyngeal arches, which are transient medial and lateral outgrowths of cranial tissue [4–6] (Fig. 10.1). These craniofacial structures develop into nerves, muscles, cartilage, bone, and connective tissue, including the body's primary sense organs and necessary for undisturbed feeding, respiration, and facial expression. The human head and face are anatomically complex structures that form during embryogenesis, from the FNP and the PAs (pharyngeal arches). The FNP gives rise to the forehead and the nose, while the paired PAs give rise to the lower face (the jaw), the neck, and part of the upper thorax (Fig. 10.2). Pharyngeal arch development is dependent upon a multipotent, migratory population of neural crest cells, which generate most of the bone and cartilage of the head and face [7–10]. Since the discovery of the neural crest, the special ability of these cells to function as a source of species-specific pattern has been clearly recognized during the last decades. Initially, this observation arose in association with chimeric transplant experiments among differentially pigmented amphibians, where the neural crest origin for melanocytes had been duly noted. Shortly thereafter, the role of cranial neural crest cells in transmitting species-specific information on size
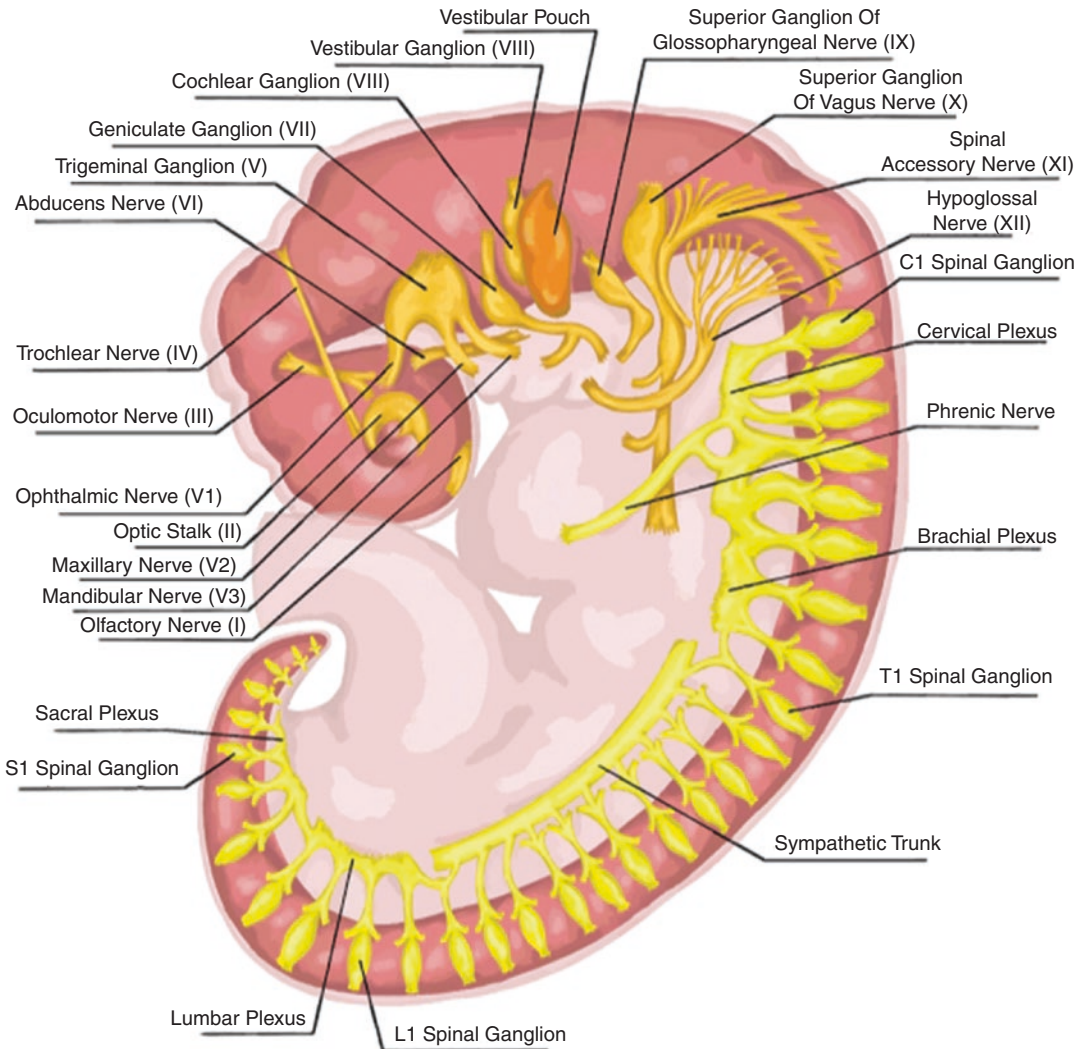
Fig. 10.1 Embryologic body development with corresponding nerve distribution. *Source: Reprinted from stihii/ Shutterstock.com with permission*

and shape to the pharyngeal arch skeleton as well as in regulating the timing of its differentiation became readily apparent [11–13].

The basic structure of the frontonasal prominence and the arches is similar in higher species (Fig. 10.3). The head and neck originate from six embryonic structures called the pharyngeal apparati, which resemble the branchial apparatus in fish [14]. Each pharyngeal apparatus comprises a pouch, an arch, a groove, and a membrane. In the fourth week of gestation, neural crest cells migrate from the neural tube to begin the development of the pharyngeal arch ectomesenchyme [12, 13]. Each arch has three layers (endoderm, mesenchyme from ectomesenchyme and mesoderm, and ectoderm), which produce the four primordial components: muscle, artery, nerve, and cartilage. Internally, all these structures are lined with endoderm, forming the pharyngeal pouches (Fig. 10.4). Concerning branchial arch diseases, the third layer between the ectoderm and endoderm epithelia is of importance [14–16]. This layer is composed of neural crest cells (NCCs) in the frontonasal prominence, whereas in the pharyngeal arches the mesenchymal core is composed of NCC and mesoderm.
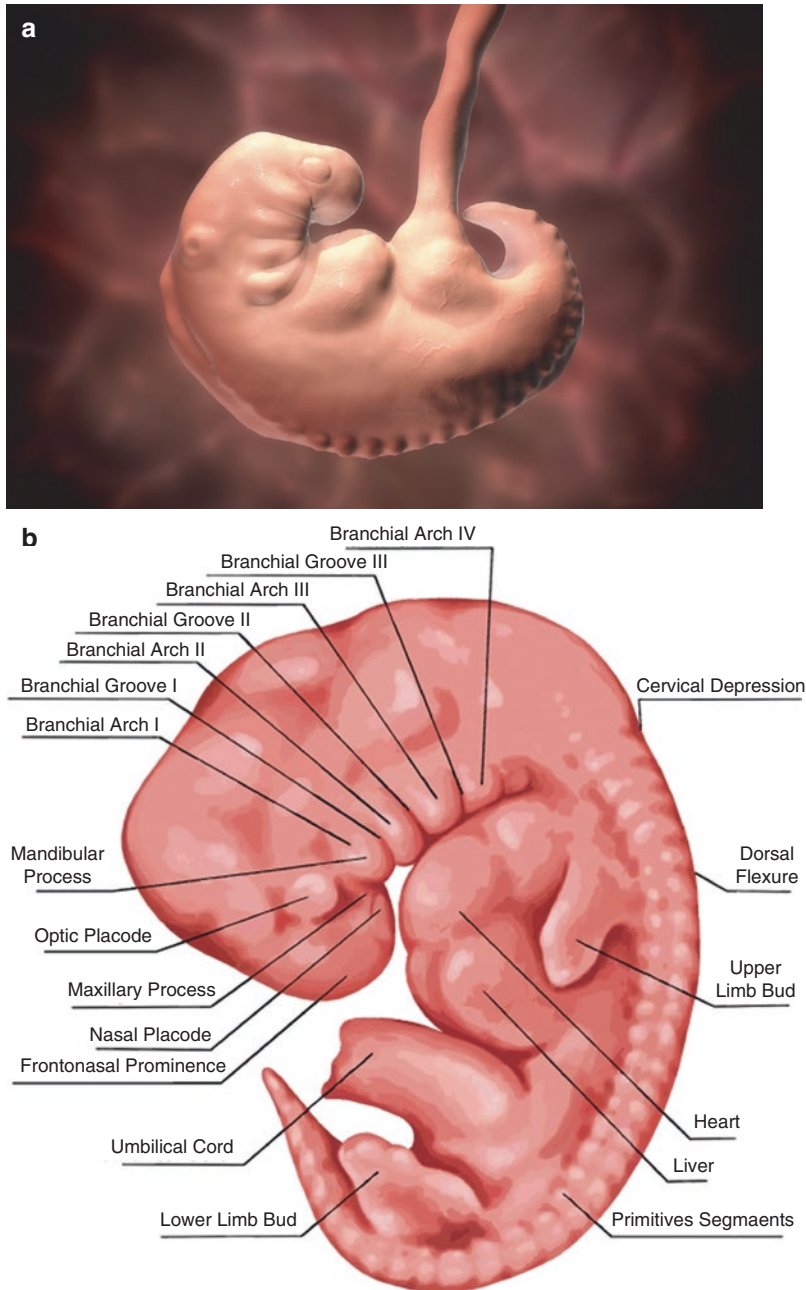
Fig. 10.2 Body and face development. (**a**) Schematic drawing of embryo with umbilical cord. (**b**) The anatomical distribution of the frontonasal prominence, the branchial arches, and the body and limb processes. *Source:* *Reprinted from a: Kateryna Kon/Shutterstock.com, b: stihii/Shutterstock.com*

The number of PAs is species dependent and may vary from 4 to 9. For example, in mammals there are 5 pairs of PAs (Fig. 10.5), numbered 1, 2, 3, 4, and 6 (as the fifth PA disappears almost as soon as it forms), while zebrafish possesses 7 PAs. However, in each case they develop sequentially in a cranial to caudal manner and are separated by a cleft and pouch which appose each other. The first PA which is also called the mandibular arch appears first,
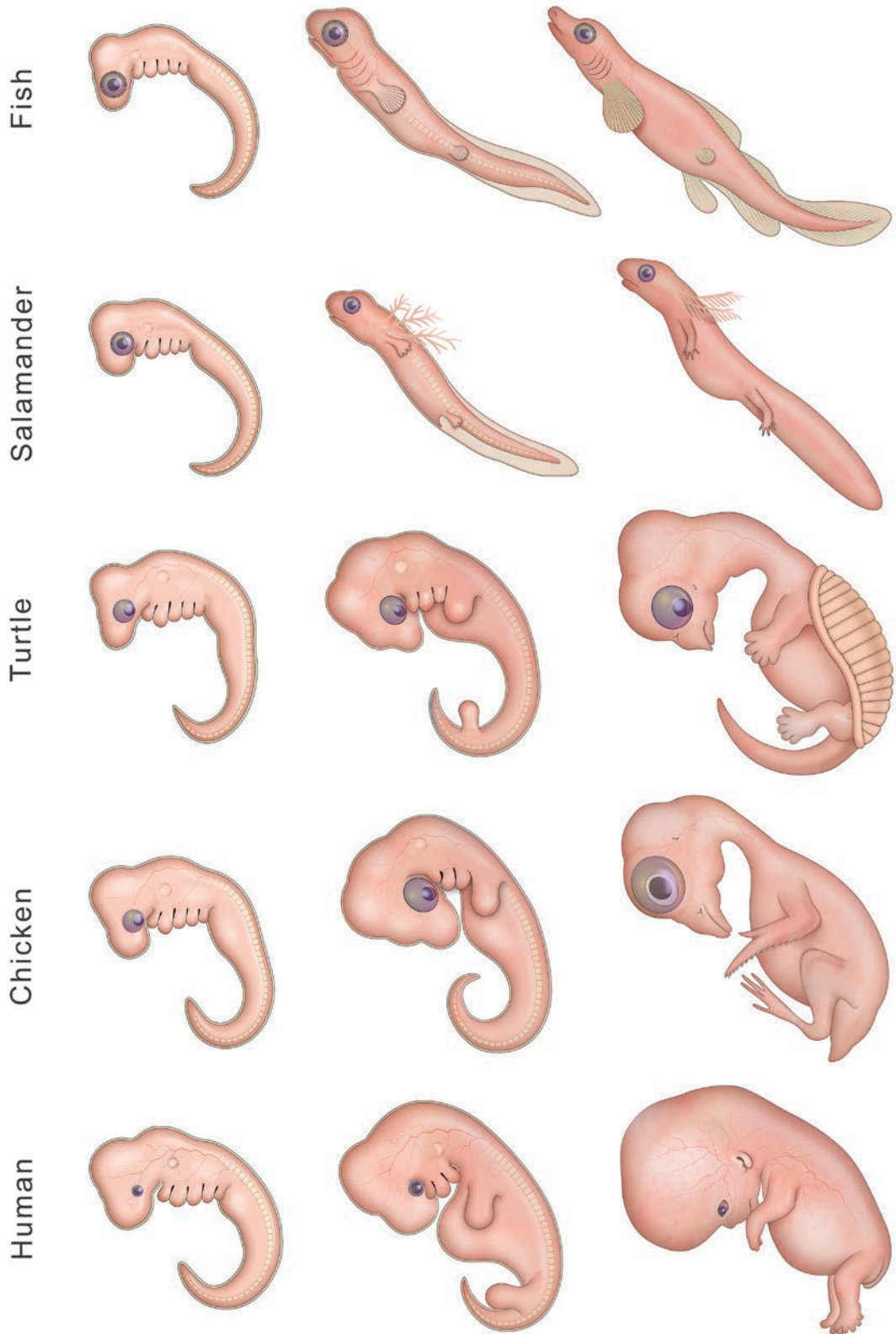
Fig. 10.3 The embryologic development is highly conserved in higher species. *Source: Reprinted from Aldona Griskevicience/Shutterstock.com with permission*

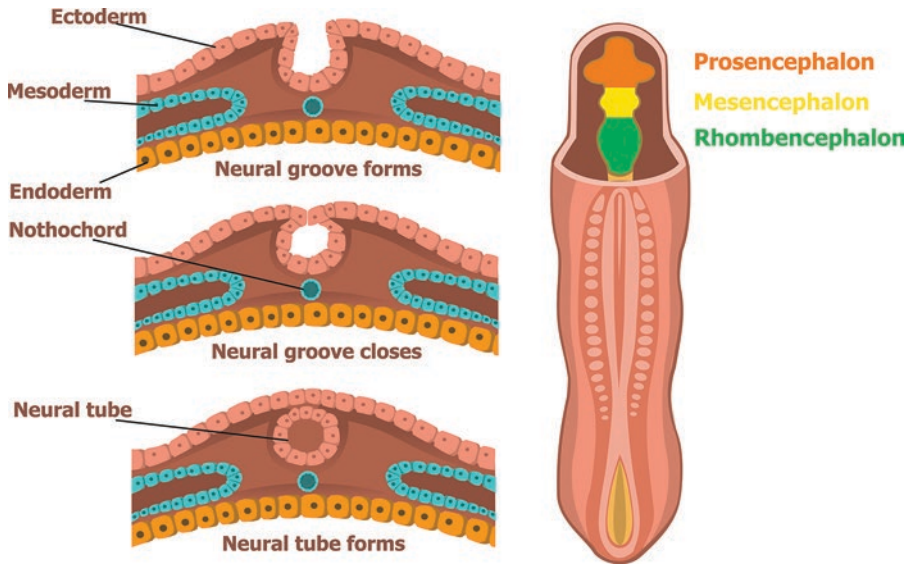**Fig. 10.4** Appearance of the neural groove and somites with the brain *Anlage. Source: Reprinted from Systemoff/ Shutterstock.com with permission*
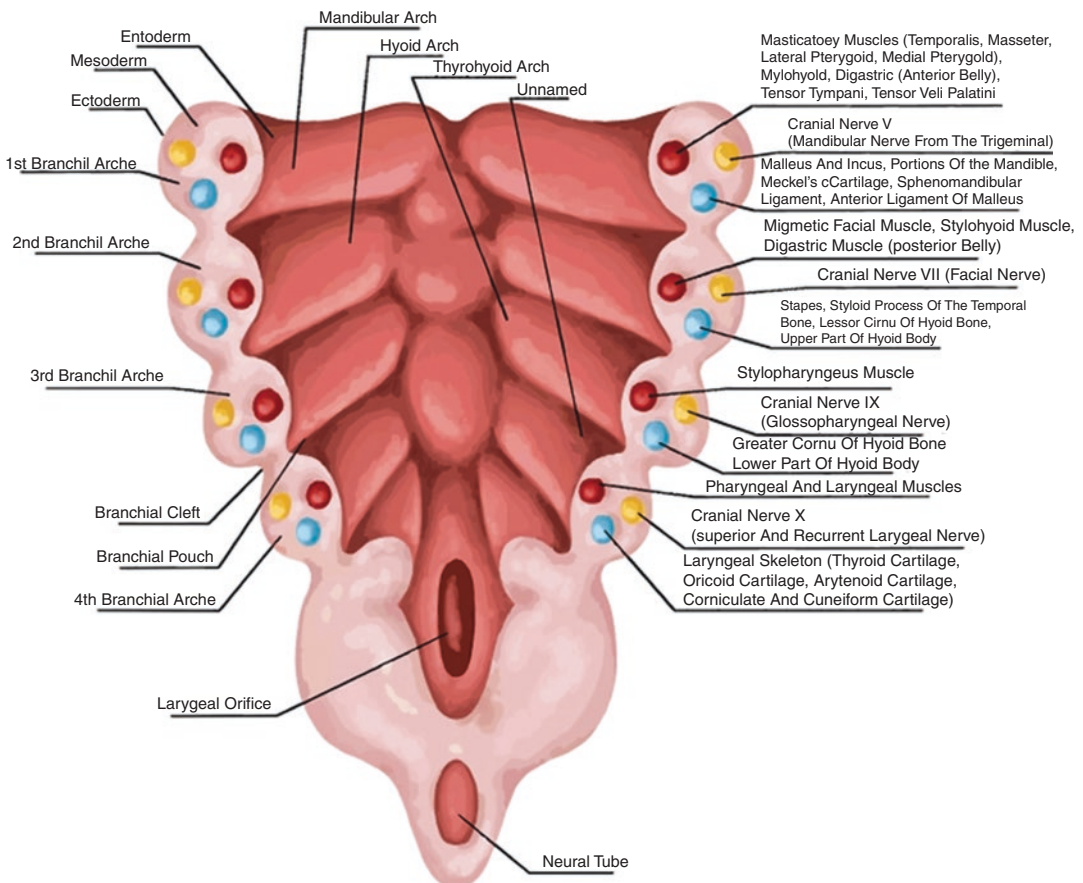

Fig. 10.5 Distribution of bones, nerves, and muscles according to the branchial arches. *Source: Reprinted from stihii/ Shutterstock.com with permission*

followed by the second PA or the hyoid arch, then the others one by one.

Concerning the primary tissue origin, it is important that the **endoderm** gives rise to viscera including the thymus, thyroid, and parathyroid glands which comprise part of the endocrine system. The **mesoderm, in contrast,** gives rise to endothelial cells and myoblasts, the progenitors of the vasculature and musculature, respectively. The **ectoderm c**an be subdivided into a lateral domain of surface ectoderm and a medial domain of neural ectoderm which gives rise to the skin and nervous system, respectively. Furthermore, the dorsal neural ectoderm that forms a boundary with the surface ectoderm also generates **NCCs** that migrate into the FNP, contributing to bones and connective tissue of the face and skull. The NCCs that colonize the PAs give rise to the bones of the jaw, the three small bones of the middle ear (malleus, incus, and sta-

pes), as well as the cartilages of the neck. They also contribute to the formation of the teeth, as NCCs give rise to the dentin-secreting odontoblasts and pulp. In contrast, the enamel is produced by oral ectoderm-derived ameloblasts. Similar to the teeth, the peripheral nervous system is also of dual cellular origin. NCCs generate sensory neurons and glia that integrate with surface ectoderm-derived cranial sensory placode generated neurons. NCCs also form mural cells, the pericytes, and smooth muscle cells that surround the endothelial cells within the great blood vessels of the head, and parts of the neck and upper thorax (for review see Frisdal and Taylor [4]). Therefore, different anatomical structures in various spatial locations in the head and neck region originate from defined arches (Fig. 10.6).

In addition to their species-specific pattern, structures likewise possess many more "species-
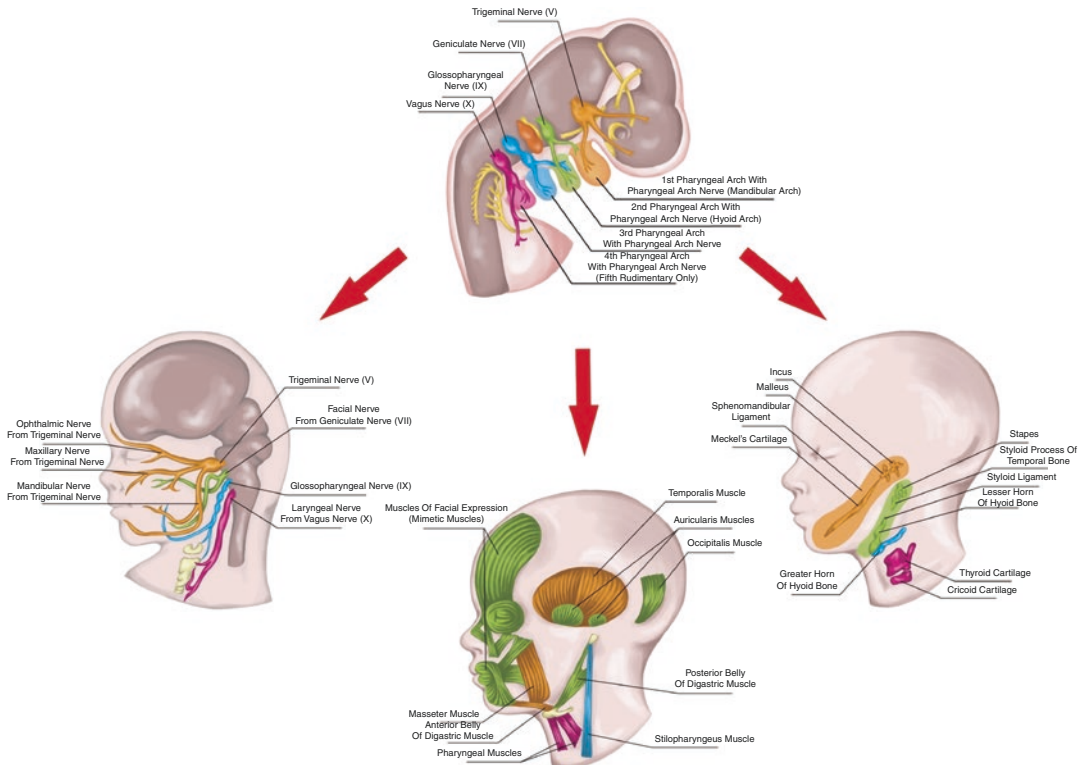

Fig. 10.6 Development of the cranial, midface, lower face, and neck structures. *Source: Reprinted from stihii/ Shutterstock.com with permission*

generic" aspects of pattern. These include their axial orientation (e.g., dorsal-ventral, medial-lateral, proximal-distal, oral-aboral), anatomical identity (e.g., upper versus lower jaw, eye versus ear), and tissue type (e.g., cartilage, bone, muscle, tendon, nerve). For the most part, epithelia in the craniofacial complex appear to supply the cues required for the establishment of generic pattern and express the factors necessary to maintain outgrowth of individual components. For example, signaling by ectodermal epithelium around the frontonasal process (i.e., the primordium that gives rise to the mid and upper face) is essential for proper expansion and orientation of skeletal elements along the dorsoventral, medio-lateral, and proximodistal axes [17]. The development of the facial region as a segmented structure of a series of reiterated structures (the arches on the exterior surface, the pouches on the interior, and a mesenchymal core) is controlled by several genes (Fig. 10.7). Between all of them, it is well known that *Hox* genes are important regulators in the spatial identity along the anterior-posterior axis of the developing verte-brate embryo. Each of the distinct segmented regions has a unique pattern of *Hox* expression, which conveys crucial positional information to the cells and tissues within it. In the context of
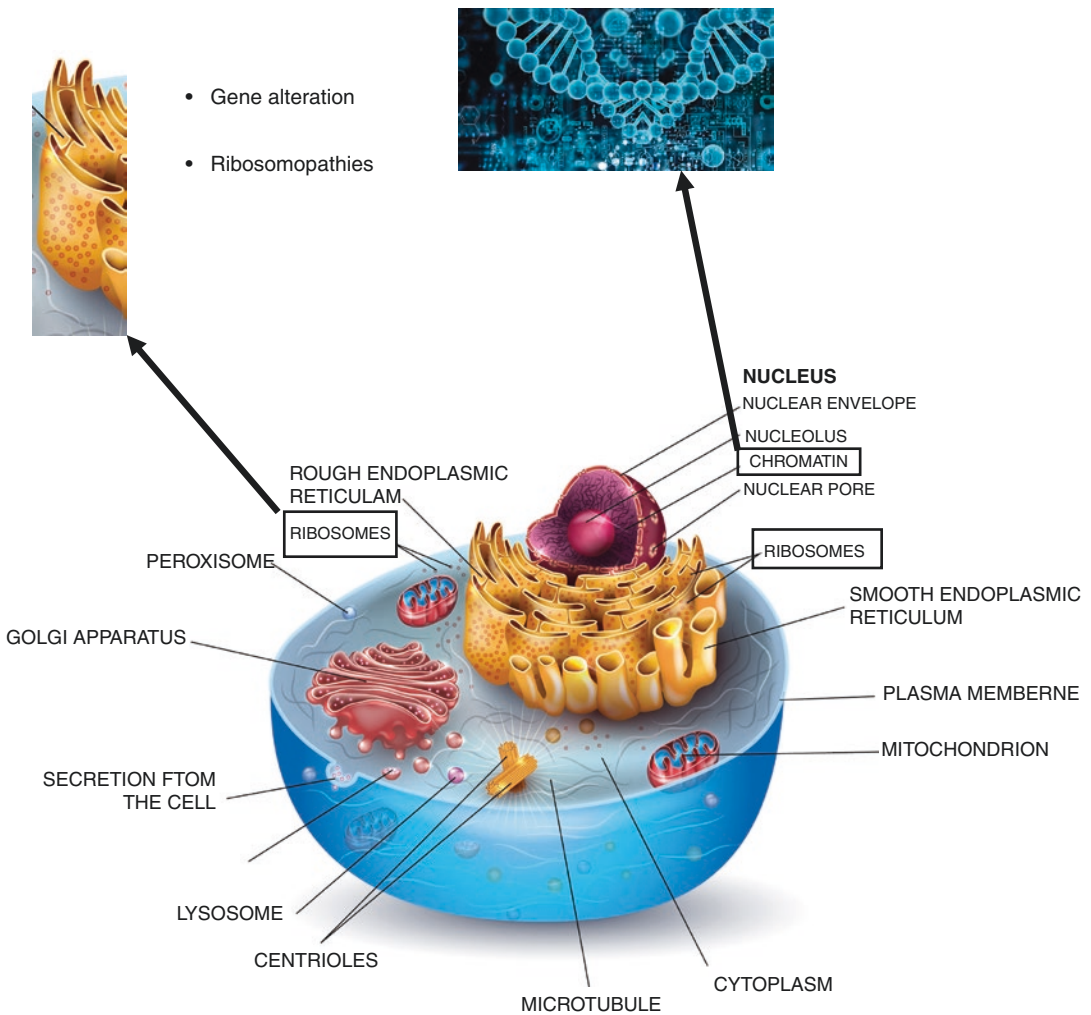

Fig. 10.7 Ribosomopathies as well as alterations in genes (HOX genes, collagen genes) are important for the cell-based origin of branchial arch diseases. *Source: Reprinted from Tefi/Shutterstock.com with permission*

pharyngeal organ development, molecular data suggest that HOXA3 is responsible for specifying organ identity within the third pharyngeal pouch, and in its absence, thymus and parathyroid organogenesis fails to proceed normally. *Dlx* genes help to establish the pattern and polarity of both neural crest cell-derived facial bones and the first branchial arch. Similar to the relationship of RA to *Hox* genes, endothelin signaling serves to regulate *Dlx* gene expression as an upstream regulator. Studies involving various *Dlx* gene deletions in mice suggest that regulation of the formation of the lower jaw is by *Dlx* transcription factor activity.

Fibroblast growth factor (Fgf) is another signaling regulator that plays a role in pharyngeal segmentation and lateral migration of endodermal cells. This process helps to facilitate the formation of pharyngeal pouches through evagination of the endoderm tissue toward the ectoderm. This process of endodermal tissue migration is referred to as "outpocketing" and is crucial for branchial arch segmentation through the approximation of endoderm and ectoderm.

10.3 Tissue and Organs Involved in Branchial Arch Diseases

Nearly all tissues in the head and neck region can be affected by the mis-development of branchial arches. Some syndromes have a unilateral involvement, whereas others present with bilateral involvement. Clinical manifestations are present in different regions of the skull and face. Additionally, phenotypic variability is common in these disease entities. Whereas some individuals have subtle facial involvement (e.g., slight facial asymmetry), others have severe involvement of multiple tissues and organs. The clinical extent of these malformations includes the skull base, the midfacial region, the mandible, and the neck (Fig. 10.8). Involved tissues and organs comprise bones of the neurocranium and the viscerocranium, the eye, the oral region, the jaws, and cranial nerves. Table 10.1 indicates the alteration of normal anatomy. The involvement of the alteration concerning branchial arch diseases is tissue and location specific [14].
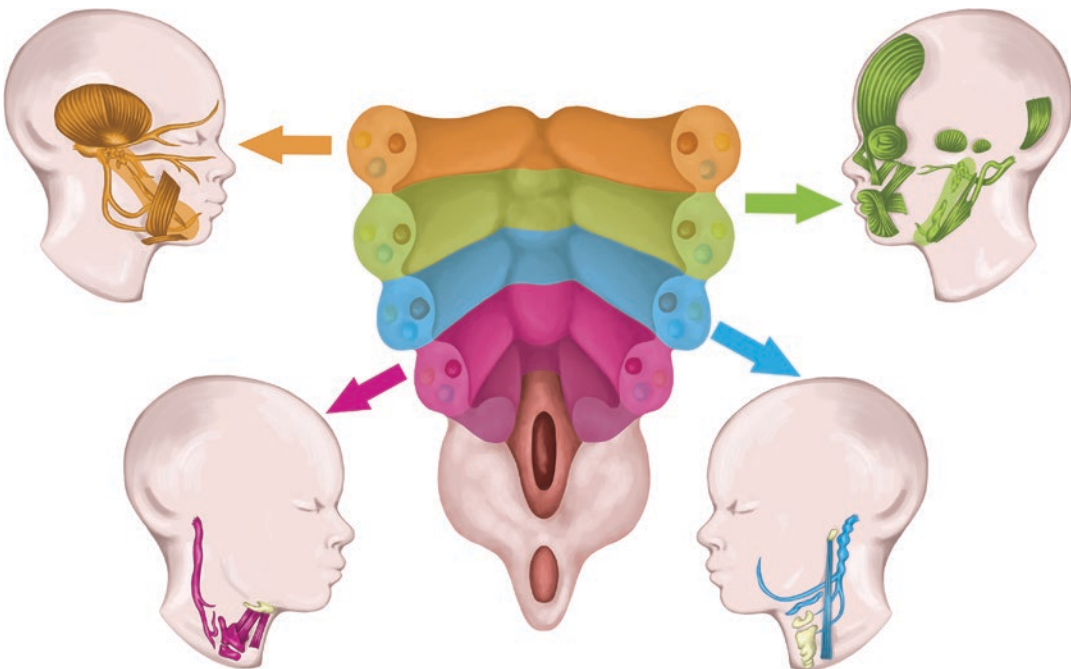

Fig. 10.8 Branchial arches and the corresponding facial structures. *Source: Reprinted from stihii/Shutterstock.com with permission*

Table 10.1 The tissues and organs that are typically mis-developed in branchial arch diseases

Skull
• Asymmetry of the skull base
• Deformed external auditory canal
• Deformed middle ear
• Deformed internal ear
Jaw
• Midface hypoplasia (underdevelopment of the midface, usually asymmetric)
• Ankylosis (limited opening of the mouth)
• Malocclusion
Eye
• Epibulbar dermoid
• Vertical displacement of the orbit
• Microphthalmia/anophthalmia (rare)
• Coloboma of the upper eye lid and/or iris
Oral region
• Macrostomia (lateral oral clefting). Unilateral macrostomia is the most common form of facial clefting associated with CFM, though all types of clefts can be observed
• Cleft lip and/or palate
Skeleton
• Malformed and/or fused cervical vertebrae are common, though anomalies can be noted throughout the spine
• Hemivertebrae are also common
Cranial nerves
• Facial palsy (unilateral or bilateral involvement of either part or all branches of cranial nerve VII)
• Sensorineural hearing loss
• Asymmetric palatal elevation
• Impairment of extraocular movements

10.3.1 Anatomical Involvement

10.3.1.1   Bones

Included in branchial arch diseases are bones of the skull base and the midfacial and lower facial region (nasal bones, zygomatic bone, jaws) (Fig. 10.9). The bones of the skull (petrosal bone and part of the zygoma) are altered. The jaw is composed of the maxilla and dentary bones, which define the upper and lower jaw, respectively. These two bones articulate to facilitate mastication, respiration, and vocalization. The jaw is formed during embryogenesis primarily from the first PA, which is composed of two paired processes known as the maxillary and mandibular prominences. The maxillary process gives rise to the upper jaw and the palate, while the mandibular process gives rise to the lower jaw. Concerning the type of ossification, two types of ossification, intramembranous and endochondral, are present. During intramembranous ossification, NCCs differentiate directly into functional osteoblasts, which induce an osteoid matrix that becomes a center of ossification. The maxilla and dentary bones undergo direct ossification of NCCs and are therefore classified as membrane or dermal bones.

In endochondral ossification, NCCs initially form a cartilage template, which is subsequently replaced by osteoblasts. Two such cartilages derived from the first PA are Meckel's cartilage, in the mandibular prominence, and palatopterygoquadrate, in the maxillary prominence. The malleus which is derived from Meckel's cartilage, together with the anterior ligament of the malleus and the sphenomandibular ligament, collectively contributes to the temporomandibular joint. The palatopterygoquadrate gives rise to the alisphenoid, a bone that is part of the orbital wall, and it also gives rise to the incus. Reichert's cartilage of the second PA forms the third middle ear bone known as the stapes.

10.3.1.2   Muscles

Muscles of the face head origin from different PAs. Concerning their function, some muscles of the face control facial expression, others control mastication, and others control the movement of the eyes and lips. All of them are derived primarily from the mesodermal cores of the corresponding PA (Fig. 10.10). In adults, the muscles of the face can be categorized by their function. For example, the muscles that have a role in mastication are derived from the first PA mesoderm, while the muscles that govern facial expression are derived from the second PA mesoderm.

10.3.1.3   Nerves

Among the 12 pairs of cranial nerves (Fig. 10.11) (olfactory n. (I), optic n. (II), oculomotor n. (III), trochlear n. (IV), trigeminal n. (V), abducens n. (VI), facial n. (VII), vestibulocochlear n. (VIII), glossopharyngeal n. (IX), vagus n. (X), accessory
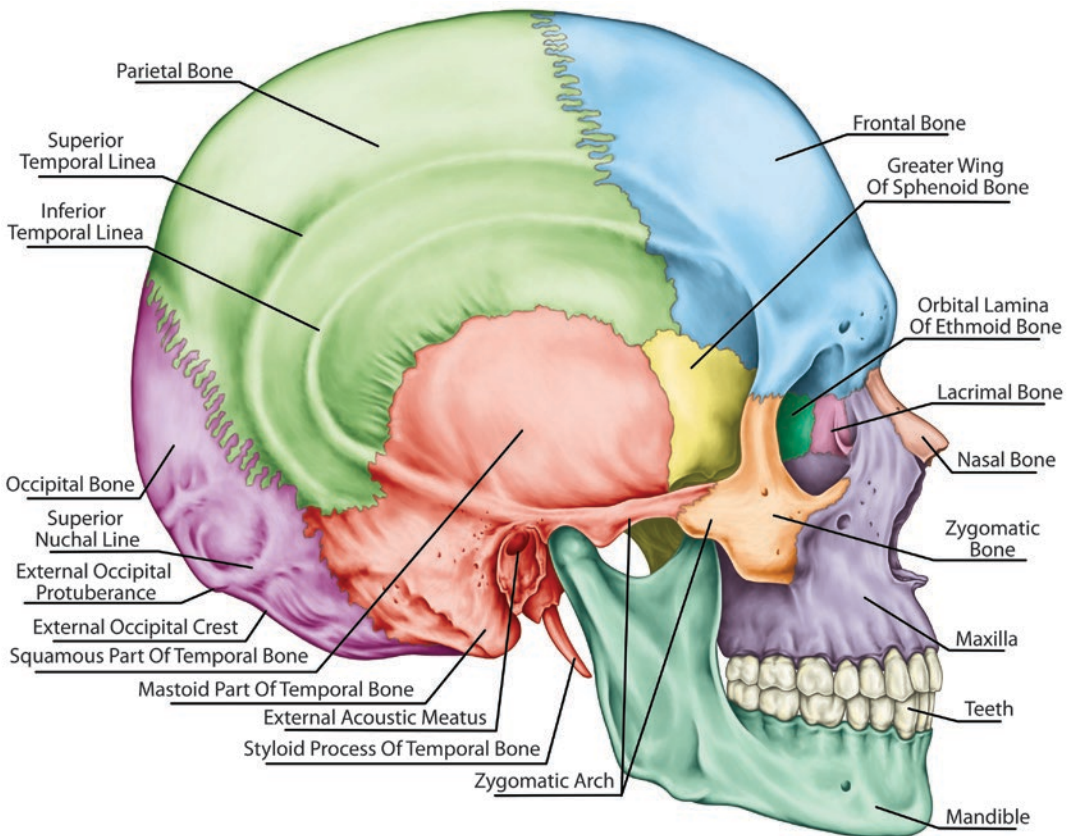
Fig. 10.9 The bones of the human skull. *Source: Reprinted from stihii/Shutterstock.com with permission*

n. (XI), and hypoglossal n. (XII)), 4 invade the PA to innervate muscles derived from the mesoderm core of the corresponding PA. The **trigeminal** (V), **facial** (VII), **glossopharyngeal** (IX), and **vagus** (X) invade the first, second, third, and fourth PA, respectively. These nerves are involved in branchial arch diseases to various extents.

10.3.2 Sensory Organs (Eyes, Ears, Tongue)

10.3.2.1 Ears

The ears are important for balance and hearing and it is derived in part from the otic vesicle which forms dorsal to the second and third PAs. The pharyngeal pouch and cleft that separate the second and third PAs are crucial for the formation of the external and middle ear. The

pouch (endoderm) gives rise to the tubotympanic recess, the epithelium of the tympanic cavity, and the Eustachian tube that links the nasopharynx to the middle ear. In addition, the first pharyngeal pouch also gives rise to the tympanus, which defines the boundary of the middle ear. In contrast, the pharyngeal cleft (ectoderm) gives rise to the external auditory canal. The vestibulocochlear nerve (VIII) is derived from the otic placode and innervates the developing inner ear.

10.3.2.2 Eyes

Malformations of the orbit and eyes are based on an abnormal morphogenesis of the frontonasal and maxillary process (derived from forebrain neural crest) with abnormal development of the first and second branchial arches (derived from hindbrain neural crest).

MUSCLES OF THE FACE

SCALP
– FRONTALIS

EYE
– CORRUGATOR
– ORBICULARIS OCULI

MUSCLES OF MASTICATION
–TEMPORALIS
– MASSETER

NOSE
–PROCERUS
–NASALIS
–LEVATOR LABII SUPERIORIS ALAEQUE NASI
– LEVATOR LABII SUPERIORIS

CHEEKS
–ZYGOMATICUS MINOR
–ZYGOMATICUS MAJOR

MOUTH
–BUCCINATOR
–ORBICULARIS ORIS
– RISORIUS

NECK
– PLATYSMA

CHIN
– DEPRESSOR ANGULI ORIS
– DEPRESSOR LABII INFERIORIS
– MENTALIS

CLAVICLE
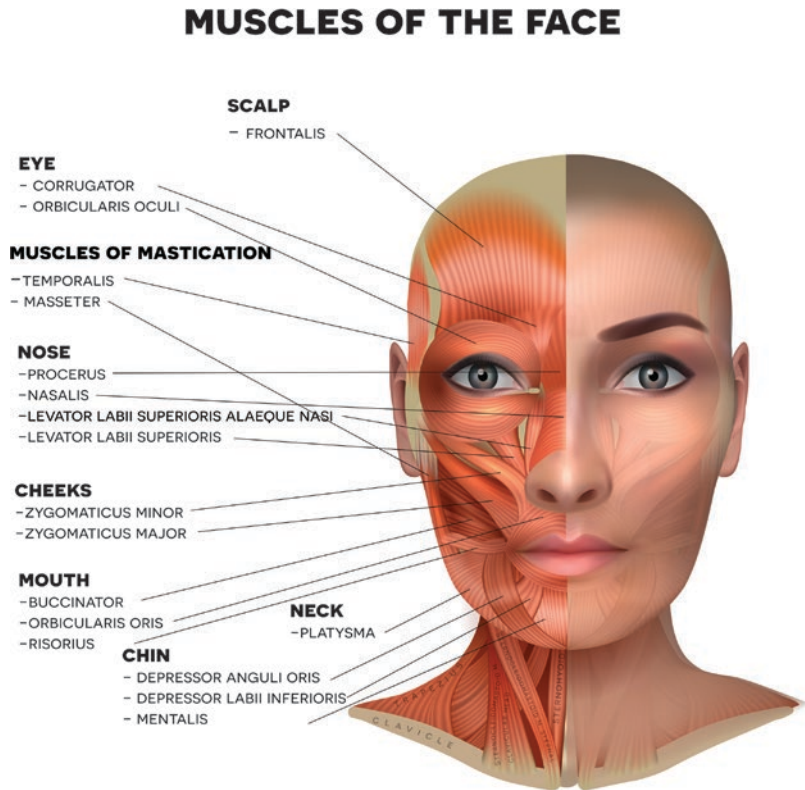
10.3.2.3   Tongue

The tongue is a particular muscle that manipulates food during mastication, perceives taste, and facilitates phonetic articulation. Its musculature derives from the mesoderm of three different PAs: the first PA mesoderm forms the body of the tongue, the second PA mesoderm is responsible for the formation of the midtongue, and the third PA mesoderm forms the root. The neuronal component of the tongue derives from NCCs; therefore, neural innervation of the tongue has a diversity concerning the location. Innervation of the anterior 2/3 of the tongue comes from the lingual (mandibular division of the trigeminal nerve V3) and chorda tympani (branch of the facial VII) nerves. The posterior 1/3 of the tongue is innervated by the glossopharyngeal nerve (IX).

10.4   Branchial Arch Syndromes

Branchial arch syndromes are clinically and etiologically heterogeneous anomalies of the craniofacial tissues. Most of them are based on NCC alterations, and others have different underlying causes like vascular disturbances or collagen synthesis alterations. These sets of malformations generally arise as a consequence of the abnormal development of the arches. Historically, they are subdivided into two subtypings: mandibulofacial dysostosis and acrofacial dysostosis. The most important syndromes (Table 10.2) are Treacher Collins syndrome, hemifacial microsomia/oculo-auriculo-vertebral dysplasia (OAV complex) with subtype Goldenhar syndrome, auriculocondylar syndrome, Stickler syndrome, DiGeorge syndrome, Pierre Robin syndrome, and acrofacial dysostosis with subtypes as follows:

– Cincinnati type
– Nager syndrome
– Miller syndrome

As the different syndromes have similar phenotypic outcomes, an overview is given on the various disease entities, with special respect to the general disease, epidemiology, underlying biological basis (genetics), and the subsequent clinical outcomes.
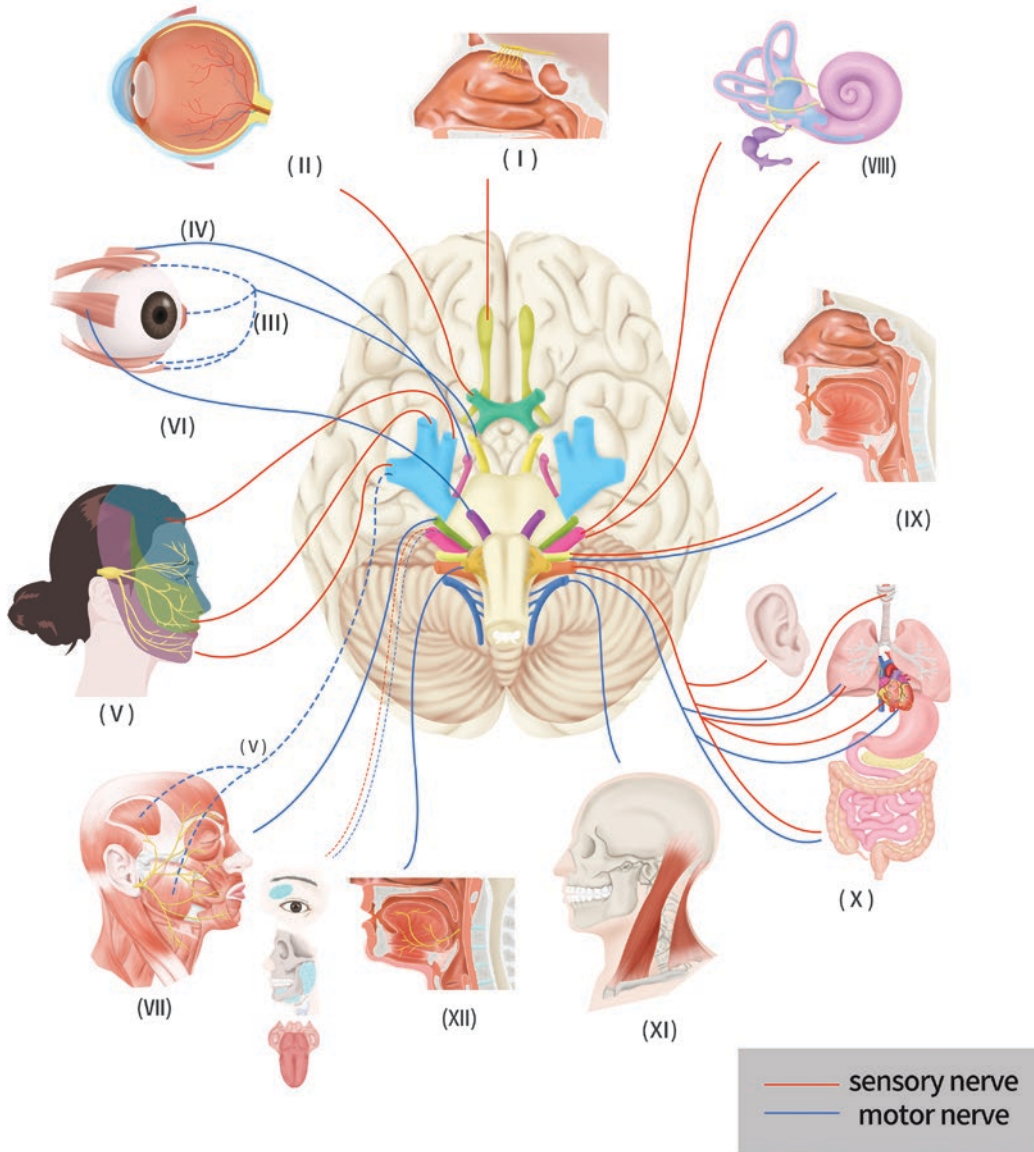
Cranial nerve

Fig. 10.11 Cranial nerves and their function (involved in branchial arch diseases are CN V, VII, IX, and X). *Source: Reprinted from Chu Kyung Min/Shutterstock.com with permission*

10.4.1 Treacher Collins syndrome

10.4.1.1   General

Treacher Collins syndrome (TCS) is a disorder characterized by deformities of the ears, eyes, cheekbones, and chin (Fig. 10.12). The degree to which a person is affected, however, may vary from mild to severe [18, 19]. Complications may include breathing problems, visual problems, cleft palate, and hearing loss. Those affected patients generally have an average intelligence. Franceschetti syndrome is synonymously used with TCS syndrome.

Table 10.2 An overview of the various branchial arch syndromes

- Treacher Collins syndrome
- Hemifacial microsomia/oculo-auriculo-vertebral dysplasia (OAV complex)
- Auriculocondylar syndrome
- Stickler syndrome
- Di George syndrome
- Pierre Robin syndrome
- Acrofacial dysostosis with subtypes
- Cincinnati type
- Nager syndrome
- Miller syndrome

10.4.1.2   Epidemiology

TCS occurs in about 1 in 50,000 people. The condition has been first described by Thompson in 1846. The syndrome is named after Edward Treacher Collins, an English surgeon and ophthalmologist, who described its essential traits in 1900. The first extensive review of the condition was published by Franceschetti and Klein in 1949, who first used the term "mandibulofacial dysostosis" and also identified its hereditary nature.
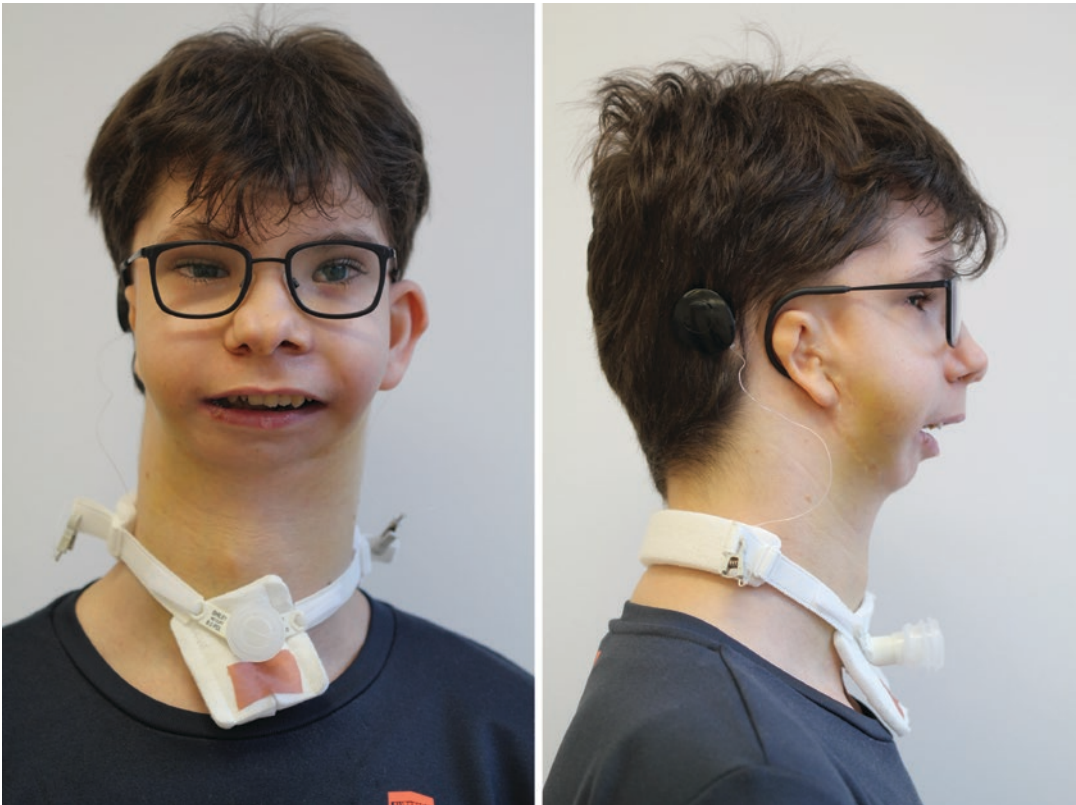

Fig. 10.12 Clinical appearance of a patient with Treacher Collins syndrome, displaying all features of the disease

Genetic basis of branchial arch diesases

Disease	Genes
TCS -	TCOF1, POLR1C/D,
Stickler-	COLL11A1/2, COLL2A1
PRS-	SOX9, GAD1, PVRL1, KCNJ2
ACF-Cincinatti	POLR1A
Nager	SF3B4
ACD-syndrome	Mutation 1p21.1-q23.3
DiGeorge	Deletion 22q11.2

Fig. 10.13 Gene involvement in branchial arch diseases. *Source: Reprinted from Pop Tika/Shutterstock.com with permission*

10.4.1.3 Genetics

A lot of genetic alterations in craniofacial diseases are well known (Fig. 10.13). TCS, for example, is usually autosomal dominant [20–23]. More than half the time it occurs as a result of a new mutation rather than being inherited from a person's parents. Forty percent of patients with TCS have a family history of the disease, and 60% of cases are seen sporadically. The occurrence of TCS is gene based presented with variable penetrance and phenotypic expression. TCS mostly arises as the result of mutations in the *TCOF1* gene [24–27]. Other involved genes may include *POLR1C* and *POLR1D*. *TCOF1* gene mutations are the most common cause of the disorder, accounting for 81 to 93% of all cases. The majority of mutations are small deletions or insertions, though splice site and missense mutations also have been identified [28–38]. *TCOF1* is found on the fifth chromosome in the 5q32 region. It codes for a nucleolar protein called treacle that is thought to be involved in ribosome assembly [39–46].

POLR1C and *POLR1D* gene mutations cause an additional 2% of cases. *POLR1C* is found on chromosome 6 at position 6q21.2 and codes for a protein subunit of RNA polymerase I.

POLR1D is found on chromosome 13 at position 13q12.2 and codes for a protein subunit of RNA polymerase III. Both of these polymerases are similar to the TCOF1 influence, important for ribosome biogenesis [47–53].

In individuals without an identified mutation in one of these genes, the genetic cause of the condition is unknown [54].

10.4.1.4 Clinical Manifestation

Symptoms in people with Treacher Collins syndrome vary. Some individuals are so mildly affected that they remain undiagnosed, while others have moderate to severe facial involvement and life-threatening airway compromise. Although facial deformity is often associated with developmental delay and intellectual disability, more than 95% of people affected with TCS have normal intelligence. The psychological and social problems associated with facial deformity can affect the quality of life in individuals with TCS.

– Skull
– Although an abnormally shaped skull is not distinctive for Treacher Collins syndrome, brachycephaly with bitemporal narrowing is sometimes observed.
– Midface/Jaws
– Facial bone hypoplasia, involving the mandible and zygomatic complex in >75% of patients, is an extremely common feature of TCS. Underdevelopment of the zygomatic bone gives the cheeks a sunken appearance. The maxilla may also be hypoplastic but sometimes can be seen as overprojecting. The nose may be broad or protruding. Choanal atresia or stenosis as a narrowing or absence of the choanae is sometimes present. The internal opening of the nasal passages may also be observed. Underdevelopment of the pharynx as a fate of the disease may narrow the airway.

– Eyes
– Other characteristic abnormalities include downward slanting of the palpebral fissures with notching of the lower eyelids and a scarceness of lid lashes medial to the defect.
– Ear
– Auricular anomalies include absent external ear canal, middle ear malformations, and pinna deformities. The external ear is sometimes small, rotated, malformed, or absent entirely in people with TCS. Symmetric, bilateral narrowing or absence of the external ear canals is also described. In most cases, the bones of the middle ear and the middle ear cavity are deformed. Inner ear malformations are rarely described. As a result of these abnormalities, a majority of the individuals with TCS have conductive hearing loss. The hearing loss is generally bilateral with a conductive loss of about 50–70 dB. Even in cases with normal auricles and open external auditory canals, the ossicular chain is often malformed.
– Oral Cavity
– Cleft palate is a common co-occurrence and may be severe. This can be accompanied by the tongue being retracted. The small mandible often results in a poor occlusion of the teeth or in more severe cases, trouble breathing or swallowing. Dental anomalies are seen in 60% of affected people, including tooth agenesis (33%), discoloration (enamel opacities) (20%), malplacement of the maxillary first molars (13%), and wide spacing of the teeth.
– Body Involvement
– Limb anomalies do not occur in TCS, which helps differentiate it from other syndromes that manifest with similar facial features.

10.4.2 Hemifacial Microsomia/Oculo-auriculo-vertebral Dysplasia with Subtype Goldenhar Syndrome

10.4.2.1 General

Hemifacial microsomia (HFM) is a common facial birth defect involving the first and second BA structures and ranks second in prevalence only behind facial clefting [55]. Males are affected more frequently than females. About 45% of patients have affected relatives, and 5–10% of them have affected siblings [56]. The phenotype is highly variable. There may be cardiac, vertebral, and central nervous system defects, in addition to craniofacial anomalies. Ear deformities occur along a spectrum from the size and shape of the external auricle to anotia. When epibulbar dermoids and vertebral anomalies are seen along with other findings of HFM, the syndrome is called Goldenhar syndrome [57]. Goldenhar [58] first described the triad of epibulbar choristomas, preauricular skin appendages, and pretragal blind-ending fistulas in association with mandibular facial dysplasia.

A variety of terms have been proposed that serve to indicate and sub-differentiate the spectrum of anomalies. Additional names of these variants include Goldenhar-Gorlin syndrome, first arch syndrome, first and second BA syndrome, lateral facial dysplasia, unilateral craniofacial microsomia, otomandibular dysostosis, unilateral mandibulofacial dysostosis, unilateral intrauterine facial necrosis, auriculobranchiogenic dysplasia, and facioauriculovertebral malformation complex. The terms and systems of classification have been reviewed multiple times [59–63]. Later patients with associated vertebral anomalies were given the classification of OAV dysplasia [58]. The combination of OAV features and microtia is termed the "OAV complex." When the features of the OAV complex are predominantly unilateral and lack vertebral anomalies and epibulbar dermoids, the condition has been called HFM. This pattern is thought to represent a variant of the expanded OAV complex [64]. Intellectual disability is not typically seen in people with HFM.

10.4.2.2 Epidemiology

Hemifacial microsomia has an incidence in the range of 1:3500 to 1:4500; it is the second most common birth defect of the face, after cleft lip and cleft palate [56]. HFM shares many similarities with Treacher Collins syndrome.

10.4.2.3 Genetics

The condition develops in the fetus at approximately 4 weeks of gestational age, when some form of vascular problem such as blood clotting leads to insufficient blood supply to the face. This

can be caused by physical trauma, though there is some evidence of it being hereditary [64, 65]. This restricts the developmental ability of that area of the face. Currently there are no definitive reasons for the development of the condition.

10.4.2.4   Clinical Manifestation

The clinical presentation of HFM is quite variable [66]. The severity may depend on the extent of the area with an insufficient blood supply in utero, and the gestational age of the fetus at which this occurs. In severe cases, multiple parts of the face may be affected.

– Skull
– Although an abnormally shaped skull is not distinctive, malformation of the external and internal ear complex leads to an asymmetric and deformed skull base at the site of involvement.
– Midface/Jaws
– In most patients, the maxilla is tilted and the mandible is deformed to different extents (Fig. 10.14). Figueroa and Pruzansky classified HFM patients, according to the mandible, into three different types [59]:
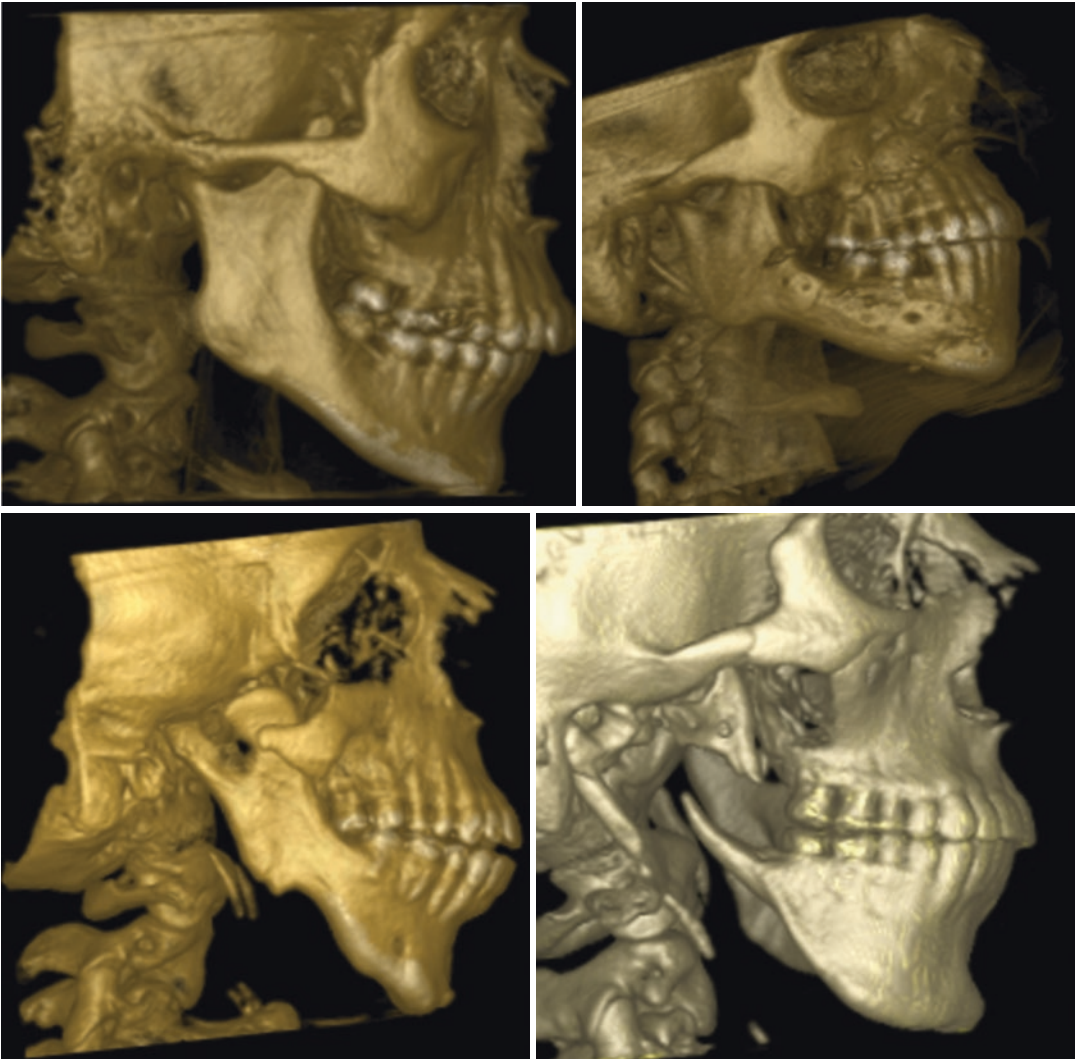
CBCT of patients with various degrees of maxillo-mandibular deformations

Fig. 10.14 Cone beam computed tomographs of the skull of patients with branchial arch diseases, demonstrating various involvements of the maxilla and mandible (from mild to severe)

- Type I: Mild hypoplasia of the ramus, and the body of the mandible is slightly affected.
- Type II: The condyle and ramus are small; the head of the condyle is flattened; the glenoid fossa is absent; the condyle is hinged on a flat, often convex, infratemporal surface; and the coronoid may be absent.
- Type III: The ramus is reduced to a thin lamina of bone or is completely absent. There is no evidence of a TMJ.
– Eyes
– In severe cases, the orbital frames are located in a tilted fashion; they are placed not perpendicular to the vertical facial axis.
– Ear
– In some people, the only physical manifestation may be a small and underdeveloped external ear. Some people with HFM may have sensorineural hearing loss and decreased visual acuity or even blindness.
– Oral Cavity
– The small mandible can result in a laterotrusion of the mandible with poor occlusion of the teeth or in more severe cases, trouble breathing or swallowing.
– Body Involvement
– Goldenhar syndrome as a particularly severe form of HFM presents to some extent extracranial anomalies. Some of the internal organs (especially the heart, kidneys, and lungs) may be underdeveloped or in some cases even absent altogether. The affected organs are typically on the same side as the affected facial features, but bilateral involvement occurs in approximately 10% of cases. Deformities of the vertebral column such as scoliosis may also be observed in Goldenhar syndrome.

10.4.3 Auriculocondylar Syndrome

10.4.3.1   General
The ACS, first described by Uuspää in 1978, is now recognized as a distinct autosomal dominant disorder. The features seen in ACS have previously been ascribed the names "Cosman ear" and the "question mark ear" [67, 68].

10.4.3.2   Epidemiology
Due to the sporadic appearance of this syndrome, epidemiologic data are inconsistent.

10.4.3.3   Genetics
Inter- and intrafamilial variability is marked, and some obligate carriers are nonpenetrant [67]. A genome-wide search of two families with ACS revealed evidence of linkage to 1p21.1-q23.3 in one of the families and non-linkage in the other [69]. These findings suggest evidence for genetic heterogeneity and the existence of at least two loci responsible for this syndrome.

10.4.3.4   Clinical Manifestation
Prominent malformed ears, with auricular clefts, mandibular condyle aplasia or hypoplasia, and a number of other auricular and oral abnormalities characterize ACS [70]. In its most severe form, there are severe micrognathia and a characteristically round facial appearance with prominent cheeks. A characteristic auricular cleft malformation is seen in ACS, which consists of a protuberant cupped pinna with a cleft or notching between the lobule and the helix. The cleft may be subtle or severe enough to detach the lobule from the helix. The anomalies can be unilateral or bilateral and are typically asymmetric. Some individuals have low-set and posteriorly rotated ears. Pre- and postauricular tags may be present. Hearing and middle ear functions are generally normal; however, sensorineural hearing loss has been reported.

Complete mandibular condyle agenesis, hypoplasia, or more subtle clinical and radiographic anomalies may be present. These findings include micrognathia, short mandibular rami, small coronoid processes, poorly formed TMJs, small condylar necks with anterior placement of the condylar articulations, and increased distances between the EACs and the posterior glenoid fossa. In some first-degree relatives of patients with ACS, the auricular malformations may be seen associated with macrognathia (type III malocclusion). Additional anomalies, somewhat specific to

ACS, include a prominent bony ridge along the lateral aspect of the mandible.

10.4.4 Stickler Syndrome

10.4.4.1 General

Stickler et al. [71] first described this autosomal dominant syndrome, also called hereditary progressive arthro-ophthalmopathy, characterized by ocular and orofacial changes, arthritic changes, and deafness. The clinical picture is highly variable and sometimes confusing, with phenotypic features varying from dwarfism/marfanoid habitus to phenotypically healthy individuals. This variability can lead to diagnostic difficulties [72].

10.4.4.2 Epidemiology

In the USA, the estimated prevalence of Stickler syndrome is about 1 in 10,000 people, but it can affect as few as 1 in 1,000,000 in other areas of the world.

10.4.4.3 Genetics

The syndrome is thought to arise from a mutation of several collagen genes during fetal development. It is a sex-independent autosomal dominant trait, meaning a person with the syndrome has a 50% chance of passing it on to each child. There are three variants of Stickler syndrome identified, each associated with a collagen biosynthesis gene [73–75]. Mutations in the COL11A1, COL11A2, and COL2A1 genes cause Stickler syndrome. These genes are involved in the production of type II and type XI collagen. Mutations in any of these genes disrupt the production, processing, or assembly of type II or type XI collagen.

Other, as yet unknown, genes may also cause Stickler syndrome because not all individuals with the condition have mutations in one of the three identified genes.

10.4.4.4 Clinical Manifestation

A characteristic feature of Stickler syndrome is a flattened facial appearance to different extents. The phenotypic appearance is caused by underdeveloped bones in the middle of the face, includ-

ing the cheekbones and the bridge of the nose. Despite the genotypic heterogeneity, the systemic features are similar for the different types. Diagnostic criteria have been proposed for type 1, comprising most patients with Stickler syndrome, which include molecular or family history data and characteristic ocular, orofacial, auditory, and musculoskeletal findings [76–78].

- Skull
- The skull is seldom involved in Stickler syndrome.
- Midface/Jaws
- The typical phenotypic facial features are caused by underdeveloped bones in the midface, including the cheekbones and the bridge of the nose. This leads to a flattened facial appearance.
- Eyes
- The most serious manifestations of the syndrome are ocular aspects, including retinal detachment, high nonprogressive myopia, and vitreoretinal degeneration. These features may lead to eventual blindness. Less common ophthalmologic features include perivascular pigmented lattice degeneration and cataracts.
- Ears
- Patients with Stickler syndrome may have congenital sensorineural, congenital conductive, or acquired conductive hearing loss. Defects of the auditory ossicles can be seen with associated congenital conductive hearing loss. Forty percent of patients show some evidence of sensorineural hearing loss, which in many patients may be clinically occult. If there is an association with CP and a high arched palate, an increased incidence of serious otitis media is found, which may lead to conductive hearing loss.
- Oral Cavity
- Some patients present with an additional cleft palate; often findings are high arched palates.
- Body Involvement
- Body involvement shows a high variability in expression. Enlarged joints, epiphyseal changes, and mild platyspondyly are typical of the disorder. Mild ligamentous laxity is seen early in life that occasionally leads to

generalized ligamentous stiffness. Osteoarthritis typically develops in the third or fourth decade. Mild spondyloepiphyseal dysplasia is often apparent radiologically. Occasional findings include slender extremities and long fingers.

10.4.5 DiGeorge Syndrome

10.4.5.1   General
DiGeorge first reported the association of the absence of the thymus with aplasia of the parathyroid glands. These observations were appreciated with variable anomalies of the cardiovascular system and craniofacial syndromes. DiGeorge syndrome, also known as 22q11.2 deletion syndrome [79], is a syndrome caused by the deletion of a small segment of chromosome 22 [80]. While the symptoms can vary, they often include congenital heart problems, specific facial features, frequent infections, developmental delay, learning problems, and cleft palate. Associated conditions include kidney problems, hearing loss, and autoimmune disorders such as rheumatoid arthritis or Graves' disease.

10.4.5.2   Epidemiology
DiGeorge syndrome is estimated to affect between 1 in 2000 and 1 in 4000 live births [81, 82]. This estimate is based on major birth defects and may be an underestimate, because some individuals with the deletion have few symptoms and may not have been formally diagnosed. It is one of the most common causes of intellectual disability due to a genetic deletion syndrome [83].

10.4.5.3   Genetics
DiGeorge syndrome is inherited in an autosomal dominant pattern [84]. It is typically due to the deletion of 30 to 40 genes in the middle of chromosome 22 at a location known as *22q11.2*. This syndrome is characterized by incomplete penetrance. Therefore, there is a marked variability in clinical expression between the different patients. This often makes early diagnosis difficult. Although there has been debate about the distinct etiologic nature of DiGeorge syndrome and velo-

cardiofacial syndrome (VCFS), there is considerable phenotypic and genotypic overlap. A 1.5- to 3.0-Mb hemizygous deletion of chromosome 22q11.2 causes VCFS [85]. This monoallelic microdeletion is considered the most common human deletion syndrome. DiGeorge syndrome has been shown to share a genetic defect with VCFS in 45–85% of cases in different series [86]. About 90% of cases occur due to a new mutation during early development, while 10% are inherited from a person's parents. It is autosomal dominant, meaning that only one affected chromosome is needed for the condition to occur [87]. Diagnosis is suspected based on the symptoms and confirmed by genetic testing [88].

10.4.5.4   Clinical Manifestation
– Skull
– Some patients present with microcephaly accompanied by a small skull.
– Midface/Jaws
– Skeletal anomalies are not uncommon and responsible for the altered facial appearance [89]. Characteristic facial features (present in the majority of Caucasian individuals) may include hypertelorism.
– Ears
– Some patients present with minor auricular anomalies. Additionally, they may present with conductive and sensorineural hearing loss.
– Oral Cavity
– Palatal abnormalities (50%), particularly velopharyngeal incompetence, submucosal cleft palate, and cleft palate, are often present. VCFS is the most frequent clefting syndrome, accounting for approximately 8.1% of children with palatal clefts seen in some centers [90].
– Body Involvement
– VCFS consists of CP, cardiac anomalies, typical facies, and learning disabilities. In a recent study, cortical areas of reduced gyration were observed, further substantiating the pattern of cerebral alterations presented with the syndrome. Almost all individuals with 22q11 deletion syndrome have behavior and/or learning problems, with >40% meeting the

criteria for either autism spectrum disorder, attention-deficit/hyperactivity disorder, or both. More than half of patients, in some series, meet the criteria for mental retardation. Less frequent features include microcephaly, short stature, slender hands and digits, minor auricular anomalies, and inguinal hernia. Cardiac anomalies have been described in 82% of patients, including isolated ventricular septal defect and tetralogy of Fallot.

Two emergent clinical situations may arise in children with VCFS on the basis of the variable associated defects of the third and fourth BAs. The first is tetany, which can be sudden and fatal, due to hypocalcemia relating to aplasia of the parathyroids. Although the absence of parathyroid gland function is rare, parathyroid dysfunction is present in approximately half of patients with VCFS. The second emergent situation is related to infections from deficiencies with the T-cell-mediated response of the immune system due to an absent or hypoplastic thymus. Immunologic evaluation is critical in affected children to identify those that may require either lymphocyte or thymus transplantation. Both of these situations require special care of patients who may require cardiac surgery.

10.4.6 Pierre Robin Syndrome/ Sequence (PRS)

10.4.6.1 General
The first publication of PRS was in 1923 by a French physician [91], describing neonates with unusually small mandibles (micrognathia), posterior displacement or retraction of the tongue (glossoptosis), and upper airway obstruction. Because incomplete closure of the roof of the mouth (CP) is present in most patients, Robin later added CP deformity as an associated feature [92–96]. Two of the main features (micrognathia and glossoptosis) cause breathing problems due to obstruction of the upper airway. A wide, U-shaped cleft palate is commonly also present.

10.4.6.2 Epidemiology
The prevalence of PRS is estimated to be 1 in 8,500 to 14,000 people.

10.4.6.3 Genetics
PRS is not merely a syndrome, but rather it is a sequence—a series of specific developmental malformations which can be attributed to a single cause. PRS may be caused by a genetic disorder. In the case of PRS which is due to a genetic disorder, a hereditary basis has been postulated, but it usually occurs due to a de novo mutation. Specifically, mutations at chromosome 2 (possibly at the GAD1 gene), chromosome 4, chromosome 11 (possibly at the PVRL1 gene), or chromosome 17 (possibly at the SOX9 gene or the KCNJ2 gene) have all been implicated in PRS [94]. Some evidence suggests that genetic dysregulation of the SOX9 gene (which encodes the SOX-9 transcription factor) and/or the KCNJ2 gene (which encodes the Kir2.1 inward-rectifier potassium channel) impairs the development of certain facial structures, which can lead to PRS [95, 96]. PRS may occur in isolation, but it is often part of an underlying disorder or syndrome [97]. Disorders associated with PRS include Stickler syndrome, DiGeorge syndrome, fetal alcohol syndrome, Treacher Collins syndrome, and Patau syndrome [98].

10.4.6.4 Clinical Manifestation
– Skull
– If a singular disease, no involvement.
– Midface/Jaws
– Studies have documented that there is also associated bimaxillary retrognathia, with reduced sagittal length of not only the mandible but also the maxilla. Although the possibility that the mandible may grow forward and partially or fully catch up during the first years of life has been discussed in the literature, recent studies have suggested that no significant catch-up growth of the mandible in PRS occurs in the first 22 months of life. The differential growth shown in these studies does not improve the size of the pharyngeal airway but does improve the relative size of the oropharynx, which can have a positive effect on breathing difficulties.

– Eyes
– If a singular disease, no involvement.
– Ears
– If a singular disease, no involvement.
– Oral Cavity
– The most prominent feature is the micrognathic state, often accompanied by a cleft palate of various extents.
– Body Involvement
– If a singular disease, no involvement.

10.4.7 Acrofacial Dysostosis

Acrofacial dysostosis describes a congenital syndrome which presents with craniofacial defects similar to those observed in mandibulofacial dysostosis (see Sect. 3.3.2.) but with the addition of limb defects.

10.4.7.1 Nager Syndrome

General
Nager syndrome is the most frequent and well-studied type of acrofacial dysostosis [99, 100]. In addition to overlapping craniofacial phenotypes with hemifacial microsomia and TCS, including downward slanting of the palpebral fissures, Nager syndrome was identified as an acrofacial dysostosis condition due to the presence of pre-axial limb defects, most commonly hypoplasia or absence of the thumbs [101, 102]. The similar phenotypes observed in Nager syndrome in comparison to other facial dysostoses, plus the small number of reported cases (n~100), make the diagnosis and identification of common mutations in Nager syndrome challenging.

Epidemiology
It is a very rare syndrome. Detailed epidemiological data are unprecise.

Genetics
Despite these limitations, recent studies identified mutations in SF3B4 in about 60% of Nager syndrome cases. Similar to TCS, Nager syndrome is rare and is primarily associated with de novo mutations, although both autosomal domi-

nant and autosomal recessive mutations have also been reported.

Clinical Manifestation
The clinical manifestations are often similar to hemifacial microsomia (see Sect. 3.3.2.) with additional limb defects.

10.4.7.2 Miller Syndrome

General
Miller syndrome, also termed post-acrofacial dysostosis (POADS), Genee-Wiedemann, and Wildervanck-Smith syndromes, is classified as an acrofacial dysostosis disorder [103–107]. Miller syndrome was the first Mendelian syndrome whose molecular basis was identified via whole-exome sequencing.

Epidemiology
It is a very rare syndrome. Detailed epidemiological data are unprecise.

Genetics
The syndrome was found to correlate with autosomal recessive or compound heterozygous mutations in dihydroorotate dehydrogenase [108, 109].

Clinical Manifestation
Similar to TCS and Nager syndromes, Miller syndrome is characterized by craniofacial abnormalities such as downward slanting of the palpebral fissures, coloboma of the lower eyelid, hypoplasia of the zygomatic complex, micrognathia, and microtia, which can lead to conductive hearing loss [110, 111]. Signifying Miller syndrome as a form of acrofacial dysostosis is the presence of post-axial limb defects, which contrasts with the pre-axial defects presented by Nager syndrome.

10.4.7.3 Cincinnati Type

General
Acrofacial dysostosis (ACF)-Cincinnati type is diagnosed in individuals with variable phenotypes ranging from mild mandibulofacial dysostosis to more severe acrofacial dysostosis [112].

Epidemiology

It is a very rare syndrome. Detailed epidemiological data are unprecise.

Genetics

Patients were found to carry a heterozygous mutation in *POLR1A*, which encodes the largest subunit of RNA polymerase I, which is responsible for transcribing rRNA [112].

Clinical Manifestation

Most patients present with variable craniofacial phenotypes similar to those observed in TCS, including hypoplasia of the zygomatic arches, maxilla, and mandible; severe micrognathia; down-slating palpebral fissures; coloboma or inferiorly displaced orbits; bilateral anotia; and conductive hearing loss. Additionally, similar to other acrofacial dysostoses, some patients present with limb anomalies, including short bowed femurs; delayed epiphyseal ossification; flared metaphysis and dysplastic acetabula; or short and broad fingers and toes.

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