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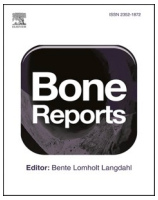

# Craniofacial disorders and dysplasias: Molecular, clinical, and management perspectives

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ABSTRACT

There is a wide spectrum of craniofacial bone disorders and dysplasias because embryological development of the craniofacial region is complex. Classification of craniofacial bone disorders and dysplasias is also complex because they exhibit complex clinical, pathological, and molecular heterogeneity. Most craniofacial disorders and dysplasias are rare but they present an array of phenotypes that functionally impact the orofacial complex. Management of craniofacial disorders is a multidisciplinary approach that involves the collaborative efforts of multiple professionals. This review provides an overview of the complexity of craniofacial disorders and dysplasias from molecular, clinical, and management perspectives.

## 1. Introduction

The genetic origin of most skeletal disorders has been identified and the craniofacial bone malformations that result have overlapping molecular, clinical, and radiographic presentations. Craniofacial skeletal disorders are generally associated with dysregulation of cell differentiation, bone patterning and development as well as alterations in bone density and ossification patterns (Foster et al., 2014). While some disorders present in the craniofacial bones symmetrical, others present asymmetrically (Luo et al., 2023). The head region is anatomically complex. All higher vertebrates share the same embryological blueprints during development that involves an integration of ectoderm, mesoderm, and endoderm germ layers. Cranial neural crest cells, a migratory population of multipotent stem cells interacts with the germ layers to form a substantial part of the bones, cartilage, odontoblasts and connective tissues of the craniofacial region and tooth morphogenesis (Brugmann et al., 2006; Cordero et al., 2011). However, the complexity involved in the integration of the germ layers and precise regulation of stem cell proliferation, differentiation, and migration to the appropriate regions of the head during development often results in craniofacial disorders and dysplasias. Craniofacial dysplasias may be associated with both lethal and non-lethal types of skeletal dysplasias and individually, majority of craniofacial disorders are rare and have different inheritance patterns (Cohen, 2003). Management of patients with craniofacial disorders is a multidisciplinary approach that involves the collaborative efforts of geneticists, radiologists, molecular biologists, surgical specialists, speech therapists and social service providers. This report is not exhaustive but focuses on clinical and radiographic presentations, histopathology, and molecular etiological factors. It also highlights common molecular and clinical features that are used to establish differential diagnosis and treatment decisions.

## 2. Classification of craniofacial skeletal disorders

Craniofacial skeletal disorders are difficult to classify because of the complex anatomical structure of the craniofacial bones as well as the genetic and phenotypic heterogeneity of the disorders that results in an overlap of clinical features of the disorders. For the purposes of this review, we classified craniofacial skeletal disorders into different groups as listed in Table 1. Some of these disorders will be highlighted.

## 3. Prominent localized craniofacial disorders and dysplasia with systemic components

### 3.1. Fibrous dysplasia and McCune-Albright syndrome

Fibrous dysplasia of bone is a rare disorder caused by gain-of-function mutations of the *GNAS* gene that encodes G-protein coupled

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receptor-associated 3′, 5′-cyclic adenosine monophosphate (cAMP)-regulating G-protein, $G_s\alpha$. In skeletal tissues, the overproduction of cAMP due to ligand-independent activation of the cAMP signaling pathway leads to abnormal differentiation of osteoprogenitor cells and formation of fibro-osseous tissues. The most common GNAS1 gene mutations are R201C and R201H (Bianco et al., 2000; Boyce and Collins, 2020). A major feature of the broad-spectrum phenotypic presentation of fibrous dysplasia is abnormal bone formation and remodeling with fibrous tissue proliferation. It can affect a single bone (monostotic fibrous dysplasia) or multiple bone (polyostotic fibrous dysplasia). Fibrous dysplasia associated with non-skeletal manifestations such as *café-au-lait* macules of the skin and hyperfunctioning endocrinopathies is known as McCune-Albright syndrome (OMIM #174800). Most notable endocrinopathies are precocious puberty, growth hormone excess, hyperthyroidism, and hypophosphatemia (Zhadina et al., 2021).

The most commonly affected bones are craniofacial bones, usually driven by growth hormone excess (Fig. 1) (Boyce and Collins, 2020). Craniofacial skeleton displays considerable expansion of the skull and jaw bones as wells as malocclusion of the teeth. Craniofacial fibrous dysplasia can cause significant facial deformities as well as vision and hearing impairments (Foster et al., 2014; Lee et al., 2012). Depending on the affected bone, fibrous dysplasia histologically displays the Chinese

**Table 1**
List of craniofacial skeletal disorders and dysplasias.

| Prominent localized craniofacial disorders and dysplasia with systemic components |
|---|
| Fibrous dysplasia/McCune Albright syndrome |
| Ossifying fibroma |
| Cemento-osseous dysplasia |
| Craniosynostosis – Non syndromic |
| Cleidocranial dysplasia |
| Hemifacial microsomia/oculoauriculovertebral dysplasia spectrum/craniofacial microsomia |
| Osteopetrosis |
| Gorham-Stout disease |
| Caffeys disease |
| **Systemic conditions associated with localized craniofacial disorders and dysplasias** |
| Osteogenesis imperfecta |
| Neurofibromatosis type 1[Von Recklinghausen disease] |
| Achondroplasia |
| Fibrodysplasia ossificans progressive |
| Filamin B Disorders |
| Gnathodiaphyseal dysplasia |
| Oculodentodigital dysplasia |
| Hypophosphatasia |
| **Syndromic lesions associated with craniofacial complex** |
| RASopathies |
| Parry-Romberg syndrome (Progressive Hemifacial Atrophy) |
| Craniosynostosis -Syndromic (Apert syndrome, Pfeiffer syndrome, Crouzon syndrome, Saethre-Chotzen syndrome, Muenke syndrome) |
| Cardio-facio-cutaneous syndrome |
| Capillary malformation–arteriovenous malformation syndrome |
| Stickler syndrome |
| Primrose syndrome |
| Saul-Wilson syndrome |
| Marshall-Smith syndrome |
| Loeys-Dietz syndrome |
| Gardner's syndrome |
| Pallister-Killian syndrome |
| Goldenhar syndrome |
| Binder syndrome |
| Kallmann syndrome |
| Marfan syndrome |
| Nager syndrome |
| Pierre Robin sequence |
| Van der Woude syndrome |
| Velocardiofacial syndrome |
| **Endocrine/metabolic related craniofacial deformities** |
| Growth hormone disorders and acromegaly |
| Hyperparathyroidism-jaw tumor syndrome |
| Brown tumor of hyperparathyroidism |
| Paget's disease |
| Osteoporosis |
| **Drug-Induced Craniofacial Deformity** |
| Medication related osteonecrosis of the jaw (MRONJ) |

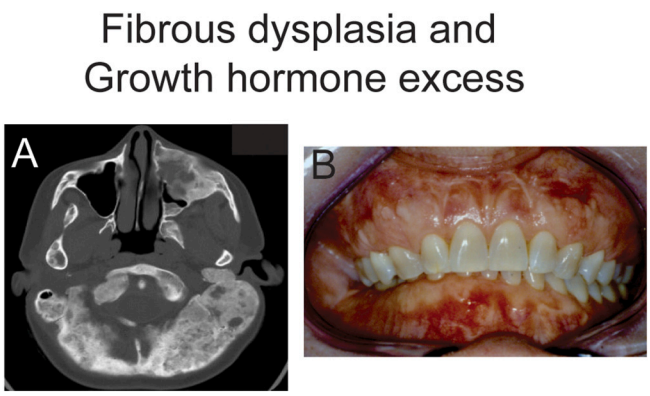


**Fig. 1.** A. Craniofacial fibrous dysplasia. The computed tomography axial view in bone window displays expansile ground-glass-like lesions in the maxilla, mandible (right ramus), and occipital bone. B. Growth hormone excess. Clinical oral photograph showing enlargement of both maxilla and mandible. The teeth are enlarged and the maxillary teeth overlap the mandibular teeth to emphasize a deep bite.

character, pagetoid or sclerotic appearance and fibrotic marrow without hematopoiesis or adipocytes (Bianco et al., 2000; Boyce and Collins, 2020). The affected bone in fibrous dysplasia displays a disorganized woven bone pattern and fibrous connective tissue matrix with abundant fibroblasts. These fibroblasts produce collagen that contribute to the fibrous nature of the dysplastic bone tissue. In some areas, evidence of excess osteoclastic activity and bone resorption can be noted histologically. Elevated levels of markers of bone turnover correlate with skeletal disease burden of fibrous dysplasia, so the therapeutic strategy for fibrous dysplasia is to target bone remodeling. Bisphosphonates and denosumab are two antiresorptive medications that have been used successfully to reduce fibrous dysplasia-associated bone pains, but disease modifying effect on fibrous dysplasia are still unclear (Boyce et al., 2012; Meier et al., 2022; Tucker-Bartley et al., 2023). Interestingly, fibrous dysplasia/McCune Albright patients have a low incidence of medication-related osteonecrosis of the jaws (MRONJ) because the fibro-osseous nature of fibrous dysplasia make it less susceptible to MRONJ (Nadella et al., 2022).

### 3.2. *Hyperparathyroidism jaw tumor syndrome and ossifying fibromas*

Hyperparathyroidism-jaw tumor syndrome (OMIM #145001) (HPT-JT) is an endocrine neoplastic syndrome characterized by parathyroid neoplasms in association with fibro-osseous jaw tumors, renal and uterine tumors (Kutcher et al., 2013; Torresan and Iacobone, 2019). HPT-JT syndrome is inherited in an autosomal dominant pattern. It results from mutations of the tumor suppressor gene *CDC73* (cell division cycle 73) also known as *HRPT2* (Bahceci et al., 2023). Parafibromin, a product of *CDC73* gene promotes cell cycle arrest and also regulate the expression of various genes through RNA polymerase-II associated factor 1 complex (Barnett et al., 2021). When mutated, the outcome is development of a benign, slowly progressive neoplasm which often presents with a jaw expansion or facial asymmetry that has well-defined borders and related malocclusion (Collins et al., 2023). Primary hyperparathyroidism is the key feature of HPT-JT syndrome but the tumor persists after parathyroidectomy and correction of patients' hypercalcemic status (Apandi et al., 2023). Infrequently, thyroid lesions, colon carcinoma, cholangiocarcinoma and pancreatic adenocarcinoma have been reported in HPT-JT syndrome (Torresan and Iacobone, 2019). Craniofacial involvement also manifests as ossifying fibromas involving the jaws, often prior to the third decade of life. About 40 % of individuals with HPT-JT syndrome present with ossifying fibromas of the jaws (Fig. 2) (Ibrahem, 2020). The ossifying fibromas develop around the tooth- bearing areas of the jaws which suggests that they arise from the

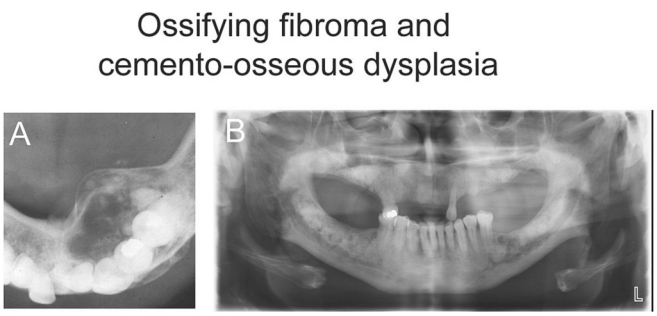


**Fig. 2.** A. Ossifying fibroma. The occlusal radiograph demonstrates the bony expansion of the left mandible and the mixed-density appearance of the expansile lesion. Note the thinning of the periosteal layer both buccally and lingually in this image. B. Cemento-osseous dysplasia. The panoramic radiograph demonstrates the multiple dense opacifications in both the maxilla and the mandible within the alveolar bone confines. The dense opacifications surrounded by radiolucent fibrous capsules are reminiscent of cemento-osseous dysplasia lesions.

periodontal ligament (Barnett et al., 2021; Torresan and Iacobone, 2019). Large sized ossifying fibromas consequently disrupt normal dentition, causing functional and aesthetic problems. Ossifying fibromas in HPT-JT can be multifocal with recurrent potential, but solitary lesions can also occur spontaneously in the jaw. There are other forms of ossifying fibromas unrelated to HPT-JT. *Juvenile ossifying fibromas* is a more aggressive fast-growing lesions in the craniofacial bones that typically occur in the first to second decades of life (Khanna and Ramaswami, 2018). *Juvenile Trabecular Ossifying Fibroma* (JTOF) is more frequent in the maxilla than mandible, it progresses rapidly and has high tendency for recurrence (El-Mofty, 2009) Juvenile Psammomatoid Ossifying Fibroma (JPOF) affects mainly the extra-gnathic craniofacial bones. The lesions are mainly located on sinonasal, orbitofrontal and ethmoid bones (El-Mofty, 2002).

Diagnosis of ossifying fibroma involves a combination of genetic, clinical, radiology and histology assessments (Barnett et al., 2021; Torresan and Iacobone, 2019). Histologically, ossifying fibroma often consists of lamellar bone as well as woven bone with peripheral osteoblastic rimming disposed in a cellular but relatively avascular, dense fibrous stroma. The mineralization may also display as lobulated collections of basophilic cementum-like material with a distinctive “brush border” that interfaces with the contiguous stroma. JTOF is composed of irregular woven bone within fibrous stroma while JPOF is composed of ossicles and psammoma-like bodies within fibrous connective tissue (El-Mofty, 2009). Radiographically syndrome-associated fibro-osseous lesion display more radiolucency, as opposed to mixed radiolucency-radiopacity observed in sporadic cases (Barnett et al., 2021; Torresan and Iacobone, 2019). The management of jaw lesions associated with HPT-JT includes excision with bone grafting and reconstruction (Torresan and Iacobone, 2019). Periodic radiographic monitoring is vital due to its high potential for recurrence and also risk of high-grade transformation of parathyroid adenoma (Ibrahem, 2020).

### 3.3. *Hemifacial microsomia/oculo-auriculo-vertebral spectrum/ craniofacial microsomia*

Hemifacial microsomia (OMIM %141400) is also known as hemifacial craniofacial microsomia or oculo-auriculo-vertebral spectrum. This condition is a sporadic or autosomal dominant complex of mainly craniofacial and vertebral anomalies. Many chromosomal anomalies have been associated with oculo-auriculo-vertebral spectrum. These include heterozygous alteration in the splicing factor 3B subunit 2 *(SF3B2)* gene on chromosome 11q13 and other reports of 22q11.2 deletions or duplications in oculo-auriculo-vertebral spectrum phenotypes. Clathrin heavy chain like 1 (*CLTCL1*), goosecoid homeobox 2 (*GSC2*),

histone cell cycle regulator *(HIRA)*, *MAPK1* (mitogen-activated protein kinase 1), T-box transcription factor 1*(TBX1)*, and yippee like 1 *(YPEL1)* have also been hypothesized as candidate genes affected in oculo-auriculo-vertebral spectrum (Tingaud-Sequeira et al., 2022). Others have suggested that there is a depletion of neural crest progenitors like SRY-box transcription factor 10 (*SOX10*) expressing cells, with consequent defects in the first and second pharyngeal arches (Timberlake et al., 2021). The hallmark of hemifacial microsomia is facial asymmetry. This asymmetry can involve the jaws, other facial bones, and soft tissues (Goncalves Ferraz et al., 2023). The ear on the affected side can be underdeveloped (microtia) or completely absent (anotia). Mandibular hypoplasia is the most prominent skeletal manifestation of hemifacial microsomia resulting in a smaller chin and jawline compared to the unaffected side. The facial nerve that controls the muscles of facial expression may be affected in hemifacial microsomia leading to weakness or paralysis of the muscles on the affected side of the face (Goncalves Ferraz et al., 2023). The vertical growth of the maxilla is limited by the short vertical ramus of the mandible. Hemifacial microsomia is a clinical feature of Goldenhar syndrome as described in the section on 'Syndromic lesions associated with craniofacial complex'. Goldenhar syndrome could be sporadic or caused by heterozygous alteration in the *SF3B2* gene on chromosome 11q13 (Jayaprakasan et al., 2023). Severe hemifacial microsomia often requires multiple orthognathic surgeries (Luo et al., 2023).

### 3.4. Cemento-osseous dysplasia

The cause of cemento-osseous dysplasia (OMIM %137575) is still unclear. The underlying mechanistic origin may relate to changes in bone structure and density resulting from disruption of Wnt/beta-catenin signaling pathway (Günhan et al., 2021). within the context of chronic trauma and jaw parafunction. Cemento-osseous dysplasia is exclusive to the jaw bone (Fig. 2) possibly due to the reparative activities of periodontal cells during deposition of reparative cement around the teeth and the high proliferative and osteogenic capacity of craniofacial skeletal stem cells that is attributed to their neural crest origin (Akintoye et al., 2006). Additionally, the periodontal fibroblasts retain their neural crest distinctive phenotypic and functional origin so cemento-osseous dysplasia becomes an outcome of cemental scar in tooth-bearing regions of the jaw (Günhan et al., 2021). Cemento-osseous dysplasia mostly occurs in females in the fourth decade of life, which suggests some modification by hormonal effects (Macdonald-Jankowski, 2008). Cemento-osseous dysplasia is mainly found in the mandible located superior to the alveolar nerve canal mostly in close contact with the tooth apex (Nam et al., 2022). Cemento-osseous dysplasia can be divided into three categories based on location and clinic-radiological features: periapical (mostly anterior), focal (mostly posterior), and florid (involving more than one quadrant of the jaw) (Nam et al., 2022). Depending on the stage, the radiographic appearance may vary from radiolucency to opacity. Hence it is challenging to differentiate cemento-osseous dysplasia from other lesions by radiography alone. Therefore, diagnosis of cemento-osseous dysplasia is made after excluding other jaw disorders such as chronic sclerosing osteomyelitis, ossifying fibroma, fibrous dysplasia and Paget's disease based on the history, clinical presentation, radiographic and histological evaluation. Typically, cemento-osseous dysplasia is asymptomatic and may be discovered as an incidental finding. Histologically, a decalcified section of cemento-osseous dysplasia shows proliferating fibrous connective with different degrees of mineralization, calcification and cementum-like material which lack osteoblastic rimming and 'brush-borders'. The bony material has various sizes and shapes, from ginger root-like patterns to smaller round formations.

### 3.5. Craniosynostosis

Craniosynostosis (OMIM #123100) is due to premature fusion of the cranial sutures resulting in distortion of cranial bone growth. A single cranial suture or variable multi-suture premature closures can occur. Craniosynostosis is sporadic in >95 % of affected families (Greenwood et al., 2014) but has strong associations with several genetic mutations. The common genetic mutations affect fibroblast growth factor receptor 1 (*FGFR1)* and *FGFR2* (Pfeitter syndrome), *FGFR2* (Apert (OMIM # 101200) and Crouzon (OMIM # 123500) syndromes), *FGFR3* (Muenke syndrome, OMIM #602849) and Twist family basic helix-loop-helix transcription factor 1 (*TWIST)* (Saethre-Chotzen syndrome, OMIM # 101400). The genetic mutation causes imbalance in Transforming growth factor, beta-1; (TGFβ1) and FGF-2 (basic FGF) levels and altered microenvironment for morphogenesis (Johnson and Wilkie, 2011). During fetal growth, there is increased osteogenic differentiation of precursor cells, increased subperiosteal bone matrix formation and early calvaria ossification. About 85 % of craniosynostosis occur as part of a syndrome while 15 % occur in isolation as a non-syndromic type. Crouzon syndrome is the most common syndromic craniosynostosis. Turribrachycephaly or bilateral coronal craniosynostosis is usually associated with syndromic forms of craniosynostosis. The genetic basis of non-syndromic craniosynostosis is still unclear but those associated with sagittal and metopic craniosynostosis should be tested for genetic mutations of *FGFR3*, SMAD family member 6 (*SMAD6*), transcription factor 12 (*TCF12*) and *TWIST1*. Other craniofacial findings in craniosynostosis include temporal bossing, strabismus, high arched palate or cleft lip and palate, sensorineural hearing loss, developmental delay, and behavioral issues. Syndromic craniosynostosis differ in craniofacial phenotypic severity. Affected individuals present with skull malformation, dysmorphic facial features that may include tower-shaped head and prominent forehead, ocular hypertelorism, proptosis, maxillary hypoplasia, down-slanting palpebral fissures, depressed nasal bridge, and syndactyly. Affected individuals may also have delayed tooth eruption, ectopic eruption, impacted teeth, supernumerary teeth, gingival hyperplasia, dental crowding, skeletal Class III malocclusion, and an open bite (Fig. 3) (Fernandes et al., 2016; Johnson and Wilkie, 2011).

### 3.6. Cleidocranial dysplasia

Cleidocranial Dysplasia Spectrum Disorder is so described because it

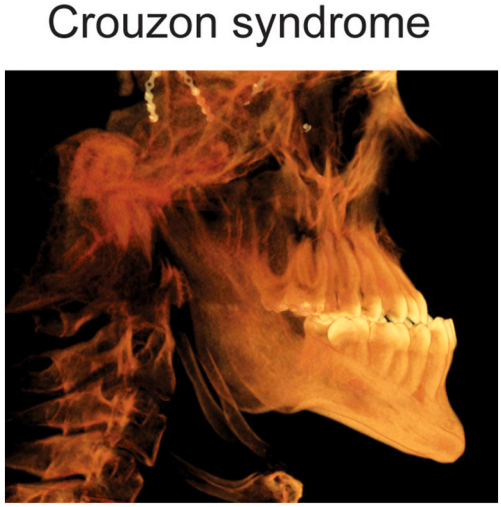


**Fig. 3.** Orofacial features of Crouzon syndrome: Cone beam-computed tomography 3D reconstruction showing the abnormal maxillofacial growth pattern in Class III malocclusion. The cranial portion of the skull is not captured in this reconstruction. Cranial synostosis is a common feature and in addition, high arched palate, posterior cross-bite, hypodontia, and crowding of teeth are commonly noted. (Case courtesy Dr. Mansur Ahmad, University of Minnesota, Minneapolis.)

has several genetic mutations but similar phenotypic expression. The most prominent variants are Cleidocranial Dysplasia – 1 (CCD1) (OMIM #119600) and Cleidocranial Dysplasia – 2 (CCD2) (OMIM #620099). CCD1 is an autosomal dominant skeletal disorder caused by heterozygous loss-of-function mutation in the runt-related transcription factor 2/Core-binding factor, runt domain, alpha subunit 1 (*RUNX2/CBFA1)* gene located on chromosome 6p21 and a critical transcriptional regulator of osteoblast and chondroblast differentiation. This results in distorted endochondral ossification because of altered *RUNX2* regulation of hypertrophic chondrocyte-specific genes throughout the process of chondrocyte maturation (Barbosa Lima et al., 2022). CCD1 variants however also exist and include CCD1 forme fruste with dental anomalies only and CCD1 forme fruste with brachydactyly. Maxillary hypoplasia with or without brachydactyly can occur following a gain of function heterozygous mutation in *RUNX2*. CCD2 variant is due to heterozygous mutation in the core-binding factor, beta subunit (*CBFB)* gene, a co-activator of *RUNX2* (Jaruga et al., 2016; Moffatt et al., 2013). Both conditions are marked by hypoplastic clavicles, short stature, late closure of the fontanel and tooth abnormalities. The significantly hypoplastic or absent clavicles implicate deficiencies of endochondral and intramembranous ossification since the clavicle ossifies embryologically through both ossification patterns. Dental/maxillofacial abnormalities are underdeveloped maxilla, relative mandibular prognathism, delayed eruption of deciduous and permanent teeth, failure of exfoliation of the primary dentition, multiple impacted permanent dentition, crypt formation around impacted teeth, multiple supernumerary teeth, crown and root abnormalities, and a high-arched palate (Daskalogiannakis et al., 2006).

### 3.7. Osteopetrosis

Osteopetrosis or marble bone disease is due to osteoclastic dysfunction characterized by generalized osteosclerosis, increased bone density, brittleness and susceptibility to pathological fractures. Osteopetrosis is associated with multiple gene mutations (Stauber et al., 2023). There are at least 16 OMIM entries for different types of osteopetrosis. Based on inheritance pattern, it can also be divided into autosomal recessive, autosomal dominant and X-linked types of osteoporosis. Defects in osteoclast development and osteoclast function lead to dysregulated bone homeostasis and osteosclerotic bone that becomes very brittle. Craniofacial features of osteopetrosis depends on the type and severity of the disease. Osteosclerosis of the cranial vault, skull base and neural foramina are common in osteopetrosis (Fig. 4). Some patients present with macrocephaly, microcephaly, frontal bossing, facial asymmetry, and mandibular prognathism. Dental abnormalities observed in osteopetrosis may include retained deciduous teeth, missing teeth, malocclusion and periodontal diseases (Ma et al., 2023). Osteopetrosis is diagnosed based on clinical evaluation, laboratory testing and radiographic findings. Routine stringent dental evaluation is recommended to prevent complications like abscesses, cysts, and osteomyelitis secondary to odontogenic infections precipitated by the altered bone morphology and anatomy (Bailey and Tapscott, 2023).

### 3.8. Gorham-Stout disease

Gorham-Stout disease (OMIM 123880) is a rare bone disorder of craniofacial bones. It is characterized by abnormal proliferation of thin-walled endothelial-lined vascular and lymphatic channels with increased numbers of osteoclasts leading to osteolysis of one or more adjoining bones. Gorham-Stout disease has also been referred to as "vanishing bone disease", or "phantom bone disease" in the literature. It is characterized by progressive and uncontrolled spontaneous bone resorption. Gorham-Stout disease does not have a clear familial pattern but generally considered to be sporadic or idiopathic. In the familial cases reported, the disease appeared to follow an autosomal dominant inheritance pattern (Angelini et al., 2022). The mandible, scapula, ribs, humerus, pelvis and femur are commonly involved (Mbaga et al., 2022). The diagnosis of Gorham-Stout disease based on clinical, histological, and radiographic findings is very complicated. The diagnosis is usually by way of exclusion of inflammatory, infectious, metabolic, and neoplastic conditions. Haffez et al (Heffez et al., 1983), suggested an 8-point diagnostic criterion for Gorham-Stout disease that included positive biopsy with angiomatous tissue, absent cellular atypia, minimal or no osteoclastic response, local progressive osteolysis, non-expansile and non-ulcerative lesion, absence of visceral involvement, osteolytic radiographic pattern, and a negative hereditary, metabolic, immunologic, infectious or neoplastic etiology. Gorham-Stout disease patients that are poor candidates for surgical intervention are treated with intensity-modulated radiation therapy and image-guided radiotherapy (Roy et al., 2022).

### 3.9. Caffeys disease

Caffey's disease (Infantile Cortical Hyperostosis) (OMIM #114000) is caused by *COL1A1* gene mutation which follows autosomal dominant inheritance pattern. It presents in early infancy and primarily affects long bones of the body, causing pain, swelling, tenderness, and fever. The symptoms usually resolve spontaneously within a few months and bone growth returns to normal. However, the jaw bones especially the mandible as well as the clavicles and scapulae, can also be affected (Khanduri et al., 2017). In some cases, Caffe's disease occurs due to somatic mosaicism, where the mutation is located in a subset of germline

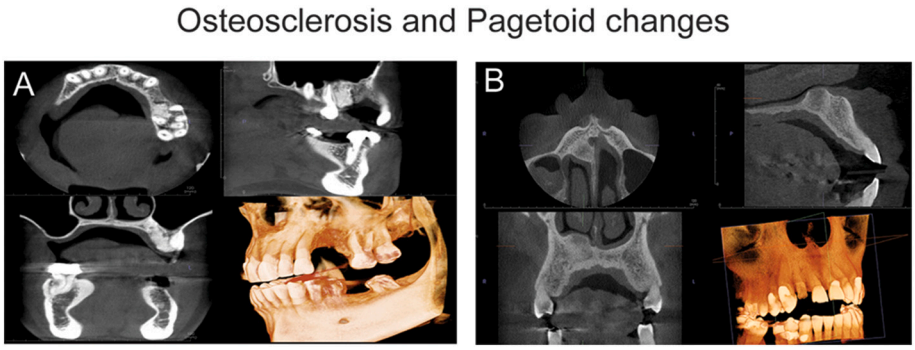


**Fig. 4.** A. Osteosclerosis. Cone beam-computed tomography multiplanar reconstructions (clockwise from top left: axial, sagittal, 3D reconstruction, and coronal views) of osteosclerosis. There is a hyperdense area just mesial to maxillary left first molar isodense to cortical bone and devoid of trabeculation suggestive of osteopetrosis. B. Localized Pagetoid Changes. Cone beam-computed tomography multiplanar reconstructions (clockwise from top left: Axial, sagittal, 3D reconstruction, and coronal views) obtained in a Paget's disease patient. There is localized bony expansion in the region of maxillary right canine-premolars elevating the floor of the right nasal fossa suggestive of a pagetoid area.

cells resulting in sporadic cases of the disease. Radiographs often show a thickening of the cortical bones in the affected area. Long bones are frequently involved. The cortical thickening is usually asymmetric and accompanied by a periosteal reaction. The periosteal reaction presents as an "onion-peel" or "wave-like" pattern characterized by multiple layers of new bone formation parallel to the long axis of the bone. There may be associated soft tissue swelling around the affected bones due to inflammation (Pinheiro et al., 2016).

## 4. Systemic conditions associated with localized craniofacial disorders and dysplasias

### 4.1. Osteogenesis imperfecta

Osteogenesis imperfecta (OMIM #166210) is an inherited connective tissue defect due to mutations of collagen type I alpha 1 chain (*COL1A1*) or collagen type I alpha 2 chain (*COL1A2*) genes that code for pro-alpha 1 and pro-alpha 2 chains respectively. The polypeptide chains produce intracellular type I procollagen, which forms extracellular type I collagen (Renaud et al., 2013). Type I collagen is found in bone, dental enamel, skin, sclera, ligaments and tendons. Mutations disrupt the spatial organization of the polypeptide chains of type I collagen thereby altering its biomechanical properties especially resistance to stretching. The craniofacial complex is also affected with a large variation in phenotype. Inheritance is mostly via autosomal dominant mode in 95 % of cases (Renaud et al., 2013). The characteristic features include short stature, skin fragility, hearing impairment, blue sclerae, multiple fractures, cardiovascular abnormalities, triangular facial form and a relatively large head. Some of the other dental problems in osteogenesis imperfecta include dentinogenesis imperfecta type I, hypodontia, crossbite and Class III occlusal relationship (Prado et al., 2023).The core radiographic features of osteogenesis imperfecta are bone loss and defects that increase susceptibility to fractures due to the disorganized bone trabeculae, large zones of woven bone and thin bone lamella. Skull radiography may show multiple intra-sutural bones that display a variegated or "paving" appearance of the cranial vault. Also, a conspicuous occipital region ("Darth Vader" appearance) or a flattening of cranial vault with transverse in-folding of cranial base ("Tam O'Shanter skull") may be seen, however, such deformities are rare (Janus et al., 2003; Renaud et al., 2013).

### 4.2. Fibrodysplasia ossificans progressiva

Fibrodysplasia ossificans progressiva (OMIM #135100) is a very rare debilitating genetic disorder characterized by heterotopic ossification of soft tissues. Mostly affected are muscles, ligaments, fascia, tendon and aponeuroses (Pignolo et al., 2022). It is an episodic progressive heterotopic ossification that occurs spontaneously or can be precipitated by soft tissue injury. Fibrodysplasia ossificans progressiva is caused by point mutation in the activin A receptor type 1 gene (*ACVR1)*, also referred to as activin receptor-like kinase-2 (*ALK2*) that encodes the bone morphogenetic protein type I receptor. Although most cases of fibrodysplasia ossificans progressiva develop spontaneously, it can also be acquired by autosomal dominant transmission.

Craniofacial features associated with fibrodysplasia ossificans progressiva are the results of heterotopic ossification of the pterygoid muscles, ossification of the stylohyoid ligament and extra-articular ankylosis of the temporomandibular joint (Carvalho et al., 2011). The restrictive movement of the temporomandibular joint at an early age causes mandibular retrognathia and maxillary overbite (Schoenmaker et al., 2022). Additionally, the dysmorphic features of the supra- and infra-orbital ridges account for the distinctive facial appearance often seen in most fibrodysplasia ossificans progressiva patients (Hammond et al., 2012). There is no distinct therapy for the craniofacial aspects of fibrodysplasia ossificans progressiva other than those associated with the disease in general. Prompt diagnosis, symptoms management and avoidance of trauma are non-therapeutic approaches. But future therapies are targeted at developing ACVR1/ALK2 inhibitors.

### 4.3. Gnathodiaphyseal dysplasia

Gnathodiaphyseal dysplasia (OMIM #166260) is a heritable bone disorder characterized by bone fragility, fibro-osseous lesions of the jaw bones and diaphyseal sclerosis of long bones (Kuroda et al., 2019; Marechal et al., 2019; Riminucci et al., 2001). The genetic basis of gnathodiaphyseal dysplasia has been mapped to chromosome 11p14.3–15.1 that harbors a missense mutation of anoctamin 5 (*ANO5)* gene and follows an autosomal dominant mode of inheritance (Otaify et al., 2018). Craniofacial anomalies are common and include, fibro-osseous lesions, osteomyelitis which often leads to periodontal/periapical abscess, tooth mobility, and delayed healing after exfoliation of tooth or exodontia. The jaw may be associated with osteonecrosis (Marconi et al., 2013). Diagnosis of gnathodiaphyseal dysplasia is based on bone histopathology and molecular techniques to detect the mutations. Maxillofacial computed tomography shows expansile, and calcified masses involving the jaw bones (Otaify et al., 2018). Histopathological findings of benign fibro-osseous lesions characterized by woven bone and acellular basophilic structures disposed in a fibrocellular stroma have been reported (Riminucci et al., 2001). Management of the craniofacial anomalies involves multiple debulking procedures to control the fibro-osseous lesions. Microsurgical mandibular reconstructions are often performed with implant-prosthetic therapy (Merlini et al., 2016).

### 4.4. Achondroplasia

Achondroplasia (OMIM #100800) is a rare genetic chondrodysplastic disorder with distinctive features of short stature, macrocephaly with frontal bossing, depressed nasal bridge and short arms and legs. It follows an autosomal dominant inheritance pattern, with full penetrance and involves mutations G1138A and G1138C in exon 10 of *FGFR3* gene. Activation of *FGFR3* stimulates several intracellular signaling pathways that include MAPK and STAT-1 pathways (Boilly et al., 2000). Reports have suggested that the STAT-1-mediated pathway of FGFR3 signaling causes decreased chondrocytes proliferation in growth plate cartilage and decreased cartilage matrix production during endochondral ossification (Sahni et al., 2001), but the impact of the MAPK pathway remains unclear. Identification of heterozygous *FGFR3* variant associated with hypochondroplasia confirms its diagnosis and distinguishes hypochondroplasia from achondroplasia which has overlapping phenotypic characteristics. Patients typically develop severe midface hypoplasia causing pseudo-prognathism and saddle nose deformity. This is thought to result from defective endochondral bone formation, while the membranous ossification continues normally (Al-Saleem and Al-Jobair, 2010). It is also suggested that mandibular growth is not affected in this condition because condylar cartilage is formed by periosteal chondrogenesis (Al-Saleem and Al-Jobair, 2010). Achondroplasia is associated with delayed dental development and Class III malocclusion with anterior open bite.

Therapy with growth hormones (Mehta and Hindmarsh, 2002) and C-type natriuretic peptides (Savarirayan et al., 2021) have shown significant benefits for improving the short stature. Surgical intervention may include foramen magnum decompression, limb lengthening, correction of genu varum, spinal canal stenosis and thoracolumbar kyphosis, as well as a combination of orthognathic surgery with orthodontic treatment (Lueveswanij and Nuntanaranont, 2002).

### 4.5. Hypophosphatasia

Hypophosphatasia (OMIM #241500) also called Rathbun's syndrome is a rare, inherited metabolic bone disease characterized by defective mineralization of bone and teeth, due to reduced serum

alkaline phosphatase (Nunes, 2007). It is caused by inactivating mutations in the alkaline phosphatase (*ALPL)* gene that encodes for tissue-nonspecific alkaline phosphatase (Villa-Suarez et al., 2021; Vogt et al., 2020). Consequently, it results in a reduction of serum alkaline phosphatase activity and increase in the accumulation of tissue-nonspecific alkaline phosphatase substrates (Vogt et al., 2020). Hypophosphatasia presents a wide array of features, ranging from death in utero to dental complications (Tournis et al., 2021). The most severe phenotypes are inherited in an autosomal recessive pattern, while the milder forms are inherited as a dominant or recessive pattern (Kiselnikova et al., 2020).

Intrauterine fetal death may complicate severe forms of hypophosphatasia due to impaired bone mineralization, while other forms may present with early loss of teeth without any musculoskeletal disorders (Kiselnikova et al., 2020). Furthermore, the organic matrix of dental hard tissues undergoes hypomineralization, subsequently affecting tooth attachment to the alveolar bone (Kiselnikova et al., 2020). Premature loss of primary teeth is a notable oral feature that results in altered masticatory function (Whyte, 2017). Other oral features commonly observed include large pulp chambers, enamel hypoplasia, tooth eruption disorders and ankylosis of primary teeth (Kiselnikova et al., 2020).

Hypophosphatasia is classified into six clinical variants based on age of onset, severity and clinical manifestations. Orofacial manifestation is seen in infantile hypophosphatasia and odontohypophosphatasia (Bianchi et al., 2020). Odontohypophosphatasia presents with dental anomalies, without associated clinical or imaging findings of the disease. There is asymptomatic atraumatic early loss of teeth without root resorption before the age of five years (Tournis et al., 2021). The average number of teeth lost before the age of five years is lower in odontohypophosphatasia relative to infantile hypophosphatasia. Panoramic dental radiographs of hypophosphatasia show enlarged pulp chambers, thin dentin, and loss of alveolar bone (Tournis et al., 2021). Hypophosphatasia is associated with persistently low serum alkaline phosphatase levels (Tang et al., 2019). Management of hypophosphatasia is determined by the presenting key features of the respective cases (Nizet et al., 2020). Presently, asfotase alfa replacement therapy is widely employed as systemic treatment for hypophosphatasia (Whyte, 2017). It has been reported that the enzyme replacement therapy at an early age in hypophosphatasia maintains the optimal level of alkaline phosphatase. Consequently, there is normal development of dental hard tissues and supporting structures of the teeth (Kiselnikova et al., 2020).

### 4.6. Oculodentodigital dysplasia

Oculodentodigital dysplasia (OMIM #164200) is a rare genetic disorder that presents with abnormal craniofacial, dental, ocular, and limb features (Choi et al., 2018; Doshi et al., 2016). It is caused by mutation of gap junction protein alpha 1 (*GJA1*) gene that codes for connexin-43. Consequently, *GJA1* mutation may result in channel misassemby or alteration of channel conduction properties (Doshi et al., 2016). Autosomal dominant form of oculodentodigital dysplasia is the preponderantly reported inheritance pattern. Associated dental anomalies include hypoplastic enamel, microdontia, multiple caries and premature tooth loss (Mubeen et al., 2011). Other features are facial dysmorphism with thin nose, microphthalmia, syndactyly and conductive deafness (Doshi et al., 2016). Management involves a multidisciplinary approach including comprehensive eye, neurological, otologic and dental evaluation. Early surveillance and detection of this disorder is vital in the prophylaxis and intervention of various manifestations of the syndrome (Doshi et al., 2016). Dental management entails preventive and restorative interventions which is personalized and specific to patient's age and affected teeth. Prophylactic procedures include caries prevention. The application of topical fluorides, pit and fissure sealants, and adhesive resin restorations should be initiated promptly. Therapeutic approach includes restoration and conservation of carious teeth, endodontic therapy, exodontia and placement of crown and space maintainers (Kayalvizhi et al., 2014).

### 4.7. Filamin B disorders

Filamin B (OMIM *603381), a protein that influences cellular cytoskeleton and signal transduction is involved in the development of the skeleton before birth. The mutations of filamin B (*FLNB*) gene result in a spectrum of mild to severe skeletal malformations. Spondylocarpotarsal synostosis syndrome and Larsen syndrome are mild; while atelosteogenesis types I and III and Piepkorn type osteochondrodysplasia are severe (Robertson, 2008). Atelosteogenesis types I and III do not have any obvious craniofacial component.

Spondylocarpotarsal synostosis syndrome (OMIM #272460) is caused by nonsense mutations (homozygosity and compound heterozygosity) in *FLNB* gene on chromosome 3p14.3 (Mitter et al., 2008). Hence, there is loss of function, which depresses TGFβ signaling thereby causing defective formation of microvasculature and severe skeletal malformations (Mitter et al., 2008). The condition is autosomal recessive and presents with dental enamel hypoplasia, and midline cleft palate. Other clinical features are short stature, scoliosis, clubfeet and sensorineural deafness (Robertson, 2008).

Larsen syndrome (OMIM #150250) is caused by at least four missense alterations and one in-frame deletion in the *FLNB* gene at locus 3p21.1–14 (Bicknell et al., 2007). Inheritance is autosomal dominant and it is marked by a distinct craniofacial appearance that include protruding forehead, malar flattening, depressed nasal bridge, and hypertelorism. Patients affected may also have midline cleft palate Other clinical features are congenital dislocation of multiple joints, clubfeet, scoliosis and spatula-shaped distal phalanges (Robertson, 2008).

Piepkorn osteochondrodysplasia is at the severe end of the phenotype continuum. Inheritance is autosomal dominant and marked by macrobrachycephaly, craniosynostosis, prominent forehead, hypertelorism, exophthalmos and occasional cleft palate. Other features are polysyndactyly with total syndactyly of all fingers and toes, flipper-like limbs, hypoplastic or absent thumbs and octodactyly (Rehder et al., 2018; Robertson, 2008). The treatment of craniofacial involvement in filamin B disorders include multidisciplinary evaluation for possible surgical intervention for the cleft palate, and conservative management of dental conditions.

## 5. Syndromic lesions associated with craniofacial complex

### 5.1. RASopathies

The RASopathies are several syndrome that result from germline mutations in genes associated with the Ras/mitogen-activated protein kinase (RAS-MAPK) pathway (Aoki et al., 2016). Dysregulation of RAS-MAPK signaling is commonly the basis of disorders of the neuro-cardio-facial-cutaneous range. The recognized driver mutations are missense alterations and few deletions of functional single amino acids. In contrast, mutations of negative regulators of the pathway include nonsense, frame shift and splice site alterations (Zenker, 2009). The RASopathies as listed by Cao et al include Noonan syndrome, Noonan syndrome with multiple lentigines or LEOPARD syndrome, neurofibromatosis type 1, Costello syndrome, cardio-facio-cutaneous syndrome, neurofibromatosis type 1–like syndrome or Legius syndrome and capillary malformation–arteriovenous malformation syndrome (Cao et al., 2017). Each RASopathy is a distinct syndrome but they share many common but distinct features (Rauen, 2013).

#### 5.1.1. Noonan syndrome (OMIM #163950)

*Noonan syndrome* (OMIM #163950) is a genetically heterogeneous disorder associated with over ten germline mutations. Affected genes include protein-tyrosine phosphatase, nonreceptor-type, 11 *(PTPN11)* (50 % of cases), SOS Ras/Rac guanine nucleotide exchange factor 1

(*SOS1)* (10 % of cases) and Raf-1 proto-oncogene, serine/threonine kinase *(RAF1)* (5–10 % of cases) (Zenker, 2009). *PTPN11* encodes SHP2 (Src homology-2 domain-containing protein tyrosine phosphatase-2) a positive regulator of Ras-mitogen-activated protein kinase (RAS-MAPK) signaling, but the underlying mechanisms are still unclear (Tartaglia et al., 2001). The syndrome is marked by relative macrocephaly, "triangular facies" with high forehead, hypertelorism, and short webbed neck. Dental anomalies include high-arched palate, posterior crossbite, open bite, multiple giant cell lesions in the jaws or soft tissues (Karbach et al., 2012), several unerupted permanent teeth and submerged/retained deciduous teeth (Uloopi et al., 2015).

#### 5.1.2. LEOPARD syndrome (Noonan syndrome with multiple lentigines) (OMIM #151100)

*LEOPARD syndrome (Noonan syndrome with multiple lentigines)* (OMIM #151100) is caused by different missense mutations in the *PTPN11* gene on chromosome 12q24 and is transmitted by autosomal dominant mode with wide variable expressivity but may arise as a spontaneous mutation. The acronym LEOPARD stands for - Lentigines multiples, Electrocardiographic anomalies, Ocular hypertelorism, Pulmonary stenosis, Anomalies of genitalia, Retardation of growth, and Deafness. It is caused by neural crest abnormality, hence, all organs originating from the neural crests (including dental tissues and some craniofacial bones) are affected (Yam et al., 2008). These are major components needed for the diagnosis of the condition. However, there are other features, some of which are decreased head circumference, mandibular prognathism, macroglossia, high-arched palate, tooth agenesis, mandibular osteolytic lesions and disrupted tooth eruption. Genetic and molecular testing are necessary for diagnosis because of the variable clinical features.

#### 5.1.3. Neurofibromatosis type 1[Von Recklinghausen disease] (OMIM #162200)

*Neurofibromatosis type 1[Von Recklinghausen disease]* (OMIM #162200) is a neuro-cutaneous-skeletal syndrome caused by alterations in the *NF1* tumor suppressor gene positioned at 17q11.2 (Wallace et al., 1990). Inheritance is autosomal dominant with numerous phenotypic expressions (Gutmann et al., 2017). The mutation in the neurofibromin 1 (*NF1*) gene leads to defective function of the neural crest cells, and hence disorders of the jaws and cranial base. *NF1* gene mutations influence formation nonfunctional neurofibromin or reduced expression of neurofibromin, thus dysregulating cellular growth and division (Abramowicz and Gos, 2014). Another probably pathogenic mechanism responsible for bone abnormalities is that the *NF1* gene mutation causes increased osteoclast proliferation, migration, adhesion, and bone resorptive capacity (Stevenson et al., 2011). The skeletal lesions in neurofibromatosis type 1 comprise one of the essential diagnostic criteria (Gutmann et al., 1997). Apart from long bone lesions, the facial skeleton is also involved and comprises diminished facial height, maxillary and mandibular abnormalities, sphenoid wing and orbital dysplasia, and rarely temporomandibular joint malformations. The radiology of the maxillofacial complex in neurofibromatosis type 1 shows bone defects due to plexiform neurofibromas, a short cranial base, retrognathic mandible and maxilla, periapical cemental dysplasia and an enlarged mandibular canal (Visnapuu et al., 2012). There may also be hypoplasia of the condyle, elongation of the coronoid process, and a notch in the posterior edge of the mandibular ramus (Avcu et al., 2023). An interesting dental finding is that individuals under 35 years of age have a lower caries susceptibility based on Decayed Missing and Filled Tooth (DMFT) index (Visnapuu et al., 2012).

#### 5.1.4. Legius syndrome (Neurofibromatosis type 1–like syndrome) (OMIM #611431)

*Legius syndrome (Neurofibromatosis type 1–like syndrome)* (OMIM #611431) presents as a mild neurofibromatosis type 1 phenotype. It is caused by germline loss-of-function heterozygous mutation in the sprouty-related EVH1 domain-containing protein 1 (*SPRED1)* gene on chromosome 15q14 (Brems et al., 2007). *SPRED1* gene is a negative regulator of RAS-MAPK signaling pathway, so the loss-of-function mutation leads to overactivation of the RAS-MAPK signal transduction cascade (Brems et al., 2012). Craniofacial features include café-au-lait macules, macrocephaly and hypertelorism.

#### 5.1.5. Costello syndrome (OMIM #218040)

*Costello syndrome* (OMIM #218040) is a rare syndrome caused by activating germline mutations in *HRAS* on chromosome 11p15. This leads to disruption of elastic fiber production because of a secondary insufficiency in the 67-kD elastin-binding protein (Hinek et al., 2000) and predisposes to growth retardation, dermatologic abnormalities, musculoskeletal abnormalities, intellectual incapacity, and a predisposition to malignancies (Rauen, 2007). Craniofacial involvement includes coarse facies, comparative macrocephaly, elevated forehead, bitemporal narrowing, shortened nose and wide nasal tip (Cao et al., 2017). Also noted in affected individuals are high-arched palate, Class III malocclusion, open bite, posterior crossbite, late tooth development/eruption and hypoplastic enamel defect (Cao et al., 2017).

### 5.2. Progressive hemifacial atrophy/Parry-Romberg syndrome

Progressive Hemifacial Atrophy or Parry-Romberg Syndrome (OMIM %141300) presents as progressive hemifacial atrophy of the skin, subcutaneous tissue, muscles, and the underlying bone. It may be associated with some systemic conditions affecting eyes, heart, and joints, including endocrinopathies (Araujo and Denadai, 2020). The craniofacial features of progressive hemifacial atrophy have been associated with mechanistic target of rapamycin kinase (*MTOR*) and DEAH-box helicase 37 (*DHX37*) gene mutations (Yu et al., 2023). The patients have facial asymmetry, dental anomalies, delayed eruption and temporomandibular joint dysfunctions. The disease starts within the first two decades of life but may eventually reach a "burn-out" phase (Ter Horst et al., 2022).

### 5.3. Cardio-facio-cutaneous syndrome

*Cardio-facio-cutaneous syndrome* (OMIM #115150) presents with characteristic multiple congenital disorders that include a distinctive facial appearance, heart defects, and mental retardation. It is associated with heterozygous mutation of the B-Raf proto-oncogene, serine/threonine kinase (*BRAF*) gene on chromosome 7q34 (Niihori et al., 2006). Other mutations that may also be responsible are found in mitogen-activated protein kinase kinase 1 (*MEK1*), *MEK2* or rarely, KRAS proto-oncogene, GTPase (*KRAS*) genes. Craniofacial features include relative macrocephaly, elevated cranial vault and forehead, hypertelorism, bitemporal narrowing, hypoplastic supraorbital ridges, depressed nasal bridge, low set, posteriorly rotated ears, high palatal arch, open bite and posterior crossbite.

Diagnosis of this condition will be reached mostly via clinical examination and genetic testing. Management is multidisciplinary and involves evaluation by several units including the orthopedics and dental specialists (Pierpont et al., 2014).

### 5.4. Capillary malformation–arteriovenous malformation syndrome

Capillary malformation–arteriovenous malformation syndrome (OMIM #608354) is characterized by malformations caused by germline mutations in RAS p21 protein activator 1 (*RASA1)* gene on chromosome 5q14.3 (Macmurdo et al., 2016). Ras GTPase-activating protein 1 is coded for by *RASA1* gene and is essential for vascular development. It negatively regulates the RAS-MAPK signaling pathway and influences cellular differentiation and proliferation. The craniofacial importance of this syndrome is that the associated maxillary and mandibular intraosseous lesions result in malocclusion, tooth mobility, and gingival

bleeding (Macmurdo et al., 2016).

### 5.5. Stickler syndrome (OMIM #108300)

*Stickler syndrome* (OMIM #108300) is a genetically heterogeneous multisystem connective tissue disorder that affects the craniofacial skeleton, eyes, inner ear, and joints. Stickler syndrome can be inherited by dominant variants of collagen genes that include collagen type II alpha 1 chain (*COL2A1*) and *COL11A1* or the recessive variants of *COL9A1*, *COL9A2*, *COL9A3*, *COL11A1* as well as non-collagen genes LDL receptor related protein 2 (*LRP2*), lysyl oxidase like 3 (*LOXL3*) and GDNF inducible zinc finger protein 1 *(GZF1*) (Baker et al., 2011; Nixon et al., 2022). There are 4 variants of the syndrome but Stickler syndrome type I is responsible for approximately 70 % of all reported cases (Hoornaert et al., 2010). Craniofacial involvement includes the following: cleft palate, broad nasal bridge, malar hypoplasia and micro/retrognathia. Other skeletal anomalies are slipped epiphysis, scoliosis, and spondylolisthesis. While adults have a normal facial profile, infants and children display retrusion of the midface. Micrognathia also tends to become less prominent over time. Management for craniofacial anomalies is therefore based on extent of deformity and compromise of vital structures like the airways and approached by a multidisciplinary team.

### 5.6. Primrose syndrome (OMIM #259050)

*Primrose syndrome* (OMIM #259050) is a rare disorder due to heterozygous missense mutation in the zinc finger and BTB domain-containing protein 20 (*ZBTB20*) gene on chromosome 3q13. The mutation affects amino acid in the first and second Zinc finger motifs, thus affecting the DNA-binding area of the transcription factor, most likely due to a dominant-negative action (Cordeddu et al., 2014). *ZBTB20* gene is involved in skeletal development and participates in terminal differentiation of the hypertrophic chondrocytes by repressing SOX9 (Zhou et al., 2015). Hence, mutation of the *ZBTB20* gene is characterized by macrocephaly, developmental delay, enlarged ears/calcified ear cartilage and a recognizable facial phenotype (frontal prominence, deep set eyes, down-slanting palpebral fissures) (Arora et al., 2020). Cystic bone lesions, cataracts, and torus palatinus develop post-puberty (Melis et al., 2020).

### 5.7. Saul-Wilson syndrome (OMIM #618150)

*Saul-Wilson syndrome* (OMIM #618150) is a rare autosomal dominant skeletal dysplasia that is due to heterozygous missense mutation of the component of oligometic golgi complex 4 (*COG4)* gene on chromosome 16q22 (Ferreira et al., 2020). COG4 controls vesicular trafficking between the Golgi and endoplasmic reticulum (Ferreira et al., 2020). Proteoglycan glycosylation, which should occur in golgi apparatus, is impaired in Saul-Wilson syndrome. It presents clinically as a markedly short stature, short distal phalanges of fingers and toes, clubfoot, and characteristic craniofacial features. The craniofacial features include: progeroid facial appearance (more conspicuous during infancy), prominent forehead, enlargement and delayed closure of the anterior fontanelle, narrow nasal bridge with convex nasal ridge and mild micrognathia. Diagnosis is via targeted analysis for the genetic mutation to confirm a clinical diagnosis. Treatment is multidisciplinary and includes management of disorders of the bone, eye, ear, and other attendant presentations.

### 5.8. Marshall-Smith syndrome

Marshall-Smith syndrome (OMIM #602535) is an autosomal dominant, rare congenital anomaly triggered by heterozygous mutations in nuclear factor I/X (*NFIX*) gene at chromosome 19p13.13. NFIX is involved in signal transduction, transcriptional activities, and replication (Martinez et al., 2015). It is marked by abnormal bone development, failure to thrive, developmental delay and dysmorphic craniofacial features that include macrocephaly, protruding forehead, shallow orbits, midface hypoplasia, irregular dentition, short nose, depressed nasal bridge, retrognathia, proptosis and blue sclerae (Shaw et al., 2010). Management requires multidisciplinary approach but the prognosis is poor in neonates and infants due to respiratory complications.

### 5.9. Loeys-Dietz syndrome (LDS; OMIM # 609192)

Loeys-Dietz syndrome (LDS; OMIM # 609192) is a genetically heterogeneous disorder of connective tissue. It is an autosomal dominant disorder caused by either de novo or familial mutations of several genes that include transforming growth factor beta receptor 1 (*TGFBR1*), *TGFBR2 TGFB2*, *TGFB3*, SMAD family member 2 *(SMAD2) and SMAD3.* It presents as aortic aneurysm syndrome associated with several systemic conditions. LDS clinical features are grouped into vascular, craniofacial, skeletal and cutaneous manifestations. LDS caused by de novo mutations display more severe craniofacial and skeletal manifestations while the familial mutations are milder (Greene et al., 2023; Velchev et al., 2021). Multiple organ systems are affected including skeletal system ('funnel chest' or 'pigeon breast', scoliosis, joint laxity, arachnodactyly, 'club foot', cervical spine malformation with or without instability), blood vessels, eyes, and skin. Craniofacial features include telecanthus, hypertelorism, strabismus, cleft palate, bifid uvula, dental crowding, malocclusion and craniosynostosis (Jani et al., 2020). Although craniosynostosis can affect any suture, it commonly involves the sagittal suture, followed by coronal suture and then metopic suture (causing dolichocephaly, brachycephaly, and trigonocephaly respectively) (Almpani et al., 2022). Management of LDS require a multidisciplinary approach with appropriate specialists, including a craniofacial cleft team.

### 5.10. Gardner's syndrome (OMIM #175100)

Gardner's syndrome (OMIM #175100) is part of the familial adenomatous polyposis spectrum of genetic mutations caused by heterozygous mutations of the adenomatous polyposis coli *(APC)* tumor suppressor gene on chromosome 5q22.2 It is inherited in an autosomal dominant fashion with variable penetrance (Chacon et al., 2007; Oliveira et al., 2016). Craniofacial involvement includes multiple osteomas of the skull and jaws that give a "cotton-wool" appearance described by others as radiopaque lesions without a translucent halo and multiple odontomas of the jaws. Dental anomalies include supernumerary, impacted and congenitally missing teeth, hypercementosis and unusually long and pointed roots of posterior teeth. Osteomas and odontomas are generally observed in the post-pubertal period (Chacon et al., 2007; Oliveira et al., 2016).

### 5.11. Pallister-Killian syndrome (OMIM #601803)

Pallister-Killian syndrome (OMIM #601803) is a rare multisystem malformation syndrome caused by a spontaneous mosaic duplication event of the short arm of chromosome 12 (12p). There is a resulting tetrasomy of 12p from the additional 12p isochromosome (Barkovich et al., 2018). The extra two copies usually appear as a single chromosome (isochromosome) (Pallister- Killian mosaic syndrome). Prominent clinically features are abnormal craniofacial appearance with neonatal frontotemporal alopecia, increased intercanthal distance, low-set ears, broad nasal bridge, high arched palate, and abnormal muscle tone (Barkovich et al., 2018). A chromosome study of skin cells that discloses 47 chromosomes including an extra small chromosome that has two short arms and no long arm (isochromosome) is needed for the diagnosis.

### 5.12. Goldenhar syndrome

Goldenhar syndrome (OMIM #164210) is a rare congenital disorder resulting from abnormal development of first and second branchial arches, The condition could be sporadic or caused by heterozygous alteration in the splicing factor 3B subunit 2 (*SF3B2)* gene on chromosome 11q13 (Jayaprakasan et al., 2023). It is typically characterized by the triad of mandibular hypoplasia, vertebral anomalies and auricular malformations. The mandible, ear, nose, soft palate, and the lip are incompletely developed on one side of the face (Gonzalez-Rodriguez and Gonzalez-Rodriguez, 2021). Hemifacial microsomia is a clinical feature of Goldenhar syndrome as described in the section on 'Prominent localized craniofacial disorders and dysplasia with systemic components'. Additionally clinical features are facial skin tags, lateral oral fissures, cardiac abnormalities and other bone defects (Muñoz-Pedroza and Arenas-Sordo, 2013). It is suggested that the abnormalities arise when fetal hemorrhage occurs around the first and second branchial arches when the blood supply of the arch's switches from stapedial to external carotid artery, hence the derivatives of the first and second branchial arches e.g. the external ear and mandible are both affected. Others have suggested that a depletion of neural crest progenitors cause the defects in the first and second pharyngeal arches (Timberlake et al., 2021),

### 5.13. Binder's syndrome

Binder type maxillo-nasal dysplasia (Binder's syndrome, OMIM % 155050) is an inherited abnormality presenting as a retruded and midface and an extremely flat nose due to hypoplasia of the mid-facial skeleton. It basically affects the anterior part of the maxillonasal complex (Bhatt et al., 2008). The etiology is still unclear because it can also occur sporadically. It has been linked to use of coumarin-based anticoagulants during pregnancy and systemic lupus erythematosus (Mazzone et al., 2019). The essential features of Binder's syndrome include a short nose, with a flattened nasal bridge, atrophy of the nasal mucosa, and aplastic frontal sinus and a tendency to develop Class III malocclusion and reverse overbite (Heo and Jin, 2018). Occasionally, microdontia of the maxillary central incisors and agenesis of the lateral incisors have also been reported in this condition (Jain et al., 2011). Binder's syndrome is also often linked to Keutel syndrome because of the similar craniofacial features (Keppler-Noreull and Wenzel, 2010). There are different approaches to the management of Binder's syndrome depending on the patient's age. Early orthodontic treatment is indicated to correct occlusal and skeletal anomalies (Heo and Jin, 2018; Jawade et al., 2022). Furthermore, bone augmentation of the hypoplastic premaxilla is crucial before the patient reaches adulthood. Multidisciplinary approach involving orthognathic, otorhinolaryngologic and reconstructive surgery are all possible treatments for Binder's syndrome. Osteotomies and cartilage or bone grafts are usually required to augment the hypoplastic skeleton in this condition (Jawade et al., 2022).

### 5.14. Kallmann syndrome

Kallmann syndrome (OMIM 308750) is a variant of congenital hypogonadotropic hypogonadism caused primarily by gonadotropin-releasing hormone deficiency. It presents with defective olfactory functions that manifest as either hyposmia or anosmia (Dzaman et al., 2017). A variety of non-reproductive non-olfactory additional anomalies including orodental defects like cleft lip or palate and hypodontia are seen in some cases of Kallmann syndrome (Hilman et al., 2023). There are different forms of Kallmann syndrome based on their mode of inheritance. Kallmann−1 (KAL-1) is caused by mutations in *KAL1* gene on chromosome Xp22.3 and inherited in an X-linked recessive pattern (Dode and Hardelin, 2010). Kallmann-2 (KAL-2) is an autosomal dominant trait, caused by mutations in *FGFR1* on chromosome 8p11 (Dode and Hardelin, 2010). Maxillofacial features of Kallmann syndrome include palatal cleft, mandibular and maxillary retrognathia. Oral and dental features manifest as tooth agenesis ranging from partial anodontia to oligodontia. In addition, microdontia and slender molar roots have also been reported (Bailleul-Forestier et al., 2010; Mølsted et al., 1997). Treatment of skeletal and dental phenotypes in Kallmann syndrome require corrective surgery and early dental restorative therapies (Luo et al., 2019).

### 5.15. Marfan syndrome

Marfan syndrome (OMIM #154700) is a heritable disorder of connective tissue associated with musculoskeletal, cardiac, and ocular lesions (Randhawa et al., 2012). It has an autosomal dominant inheritance pattern caused by mutations in In fibrillin-1 gene (*FBN1*) on chromosome 15q21. Fibrilin 1 is a structural component of the extracellular matrix (Ekure et al., 2009; Sivasankari et al., 2017). Occasionally, Marfan syndrome can result from mutation of the *TGFBR2* gene (Bollero et al., 2017). Cranial and maxillofacial features consist of narrow and dolichocephalic skull, highly arched palate, hypoplastic maxilla leading to posterior crossbite and skeletal Class II malocclusion, enophthalmos, frontal bossing and increased intercanthal distance. Pulp stones are frequent findings in dental radiographs. Temporomandibular joint dysfunctions are common due to articular capsule deformation and ligament hyperlaxity (Bauss et al., 2004). Other features include hypodontia, long narrow teeth, bifid uvula and mandibular prognathism. Oral manifestations including a high incidence of dental caries, tooth root malformation, abnormal pulp chambers with pulp stones and periodontal lesions, have been linked to Marfan syndrome (Van Camp et al., 2020). Management of Marfan syndrome is a multidisciplinary approach. From dental perspectives, the high caries index based on DMFT score and high index of gingival inflammation increase susceptibility to periodontal disease. Early orthodontic intervention is highly indicated due to many associated skeletal manifestations (Bollero et al., 2017).

### 5.16. Nager syndrome

Nager syndrome (OMIM #154400) is heritable pre-axial acrofacial dysostosis affecting the development of the face, hands, and arms. it presents with malformation of the craniofacial skeleton associated with anomalies of the thumbs and forearm resulting from developmental disturbances of the first and second branchial arches and limb buds (Abdollahi Fakhim et al., 2012; Petit et al., 2014). Craniofacial malformations include malar hypoplasia resulting in downward slanting palpebral fissures, lower eyelid colobomas, flat nasal bridge, maxillomandibular hypoplasia, micrognathia, microtia, dysplastic pinnae and conductive hearing loss (Ibrahim and Eid, 2021; Petit et al., 2014). Nager syndrome arise from splicing factor 3B subunit 4 (*SF3B4)* gene mutation mapped to chromosome 1q21 that codes for a protein linked with bone morphogenetic protein signaling (Petit et al., 2014). It is often sporadic, occasionally, autosomal mode of inheritance has been reported (Abdollahi Fakhim et al., 2012). Cleft palate is often associated, consequently causing feeding problems in infants with Nager syndrome. Furthermore, palate and velopharyngeal deformities impair vocalization and early speech activities. Severe trismus and concomitant hand deformities impair maintenance of adequate oral hygiene, predisposing to a wide array of oral health challenges (Abdollahi Fakhim et al., 2012). Partial airway obstruction from glossoptosis due to associated micrognathia, may lead to life-threatening respiratory challenges (Abdollahi Fakhim et al., 2012). Nager syndrome shares similar craniofacial features with other disorders arising from abnormal differentiation of the first and second pharyngeal arches, notably Oculo-auriculo-vertebral syndrome, Treacher Collins syndrome, and Auriculo-Condylar syndrome. However, presence of preaxial upper-limb deformities are cardinal signs of Nager syndrome (Lin, 2012). Diagnosis relies on a holistic approach encompassing thorough clinical history and physical features

with genetic screening. Imaging modalities often show detailed bone anomalies that are valuable adjuncts for diagnosis. Comprehensive management is also a multidisciplinary approach to address the wide array of associated deformities (Ibrahim and Eid, 2021). Surgical intervention is indicated to correct the micrognathia and increase mandibular mobility (Lin, 2012).

### 5.17. Pierre Robin sequence

Pierre Robin sequence (PRS; OMIM 311895) is a genetic birth defect manifesting clinically as micrognathia, glossoptosis and airway obstruction that may include cleft palate and feeding difficulties (Yekula et al., 2020; Zhang et al., 2019). About half of PRS cases are isolated, while the others are syndromic (Yekula et al., 2020). PRS is a sequence of disorders, with one abnormality resulting in the next. PRS is initiated with mandibular hypoplasia, causing posterior positioning of the tongue (glossoptosis) and increased potential for respiratory compromise. Furthermore, trapping of the base of the tongue in the nasopharynx consequently impedes palate formation, leading to palatal cleft (Hsieh and Woo, 2019; Yekula et al., 2020). Mechanical, neurological maturation and mandibular compression have all been postulated as causes of the hypoplastic mandible (Giudice et al., 2018). Sporadic PRS has been linked with mutations on chromosomes 2, 4, 11, or 17. It has been proposed that *SOX9* gene mutations may affect the development of orofacial structures, leading to sporadic PRS (Baxter and Shanks, 2023). Genes associated with natal growth, morphogenesis, and patterning implicated in PRS have been mapped to various chromosomal loci [2q24.1–33.3, 17q21–24.3, and 11q21–23.1] (Amarillo et al., 2013). PRS presents with several craniofacial anomalies and the disorder is notably associated with Stickler syndrome but less often with velocardiofacial syndrome and Treacher Collins syndromes (Gangopadhyay et al., 2012). Craniofacial manifestations include micrognathia and glossoptosis. Micrognathia identified at birth is a significant feature of the diagnosis. The hypoplastic mandibles are small in both the vertical and horizontal dimensions. These subsequently result in the decrease in the anteroposterior projection of the mandible with consequent retrogenia and glossoptosis (Gangopadhyay et al., 2012). Pierre Robin sequence is commonly associated with a wide cleft palate. Breathing and feeding difficulties occur due to the glossoptosis, micrognathia and cleft palate. Additional symptoms include repeated ear infections and natal teeth (Baxter and Shanks, 2023). Clinical findings of retrognathism and glossoptosis form the basis for diagnosis. Degree of functional disturbance assessed from the severity of feeding, respiratory and speech difficulties determine the severity of this sequence (McGhee et al., 2024). A multidisciplinary approach in the management is pertinent in view of the potential association with other syndromes (Gangopadhyay et al., 2012).

### 5.18. Van der Woude syndrome

Van der Woude syndrome (VWS; OMIM #119300) is an autosomal dominant clefting disorder associated with lower lip pits and cleft lip and/or cleft palate (Alade et al., 2020; Estevez-Arroyo et al., 2023; Gurpal-Chhabda and Singh-Chhabda, 2018). Mutations of interferon regulatory factor 6 (*IRF6*) and grainy head like 3 (*GRHL3*) genes have been implicated in VWS (Estevez-Arroyo et al., 2023). Other oral manifestations include partial anodontia, dental transposition, supernumerary tooth, taurodontism, scissors bite, anterior crossbite, temporomandibular disorder, narrow high arched palate, and ankyloglossia (Estevez-Arroyo et al., 2023). Congenital anodontia may contribute to narrowing of the dental arches, especially in the maxilla due to associated clefting that results in malocclusion and a need for orthodontic intervention (Lam et al., 2010). The clinical diagnosis of VWS is confirmed by the presence positive family history of lower lip pits and concomitant cleft lip and cleft palate (Butali et al., 2014). Multidisciplinary approach is indicated in the management of VWS for the correction of clefts and associated anomalies (Tehranchi et al., 2017).

### 5.19. Velocardiofacial syndrome

Velocardiofacial syndrome (OMIM #192430) is a genetic microdeletion syndrome characterized by a combination of cleft palate, heart defects; immune deficiencies, hypocalcemia, facial dysmorphism, learning problems and intellectual disability (AlQarni et al., 2018). It is the commonest microdeletion syndrome caused by microdeletion of DNA on a single copy of chromosome 22q11.2. Point mutation of T-box transcription factor 1 *(TBX1)* gene has been implicated in the etiology of Velocardiofacial syndrome (Bartzela et al., 2017). Craniofacial features include cleft palate, hypertelorism, short philtrum, malar hypoplasia and thin alae nasi (Wu et al., 2013). Bone disorders include a short velum, and malformed cranial base (Leveau-Geffroy et al., 2011), micrognathia (Wang et al., 2009), steep mandibular plane angle, increased anterior face height, retroclined lower incisors, and increased interincisal angle (Oberoi et al., 2011). There is associated skeletal Class II malocclusion, with a retrognathic mandible and open bite (Lewyllie et al., 2017). Orodental features include agenesis of permanent teeth, especially mandibular incisors and maxillary second premolars (Heliövaara et al., 2015). Delayed eruption of permanent teeth, with associated enamel hypoplasia and hypomineralization (Nordgarden et al., 2012) and prevalent rampant caries has been reported (AlQarni et al., 2018).

## 6. Endocrine/metabolic related craniofacial deformities

### 6.1. Growth hormone disorder and acromegaly

Acromegaly (OMIM #300943) is a rare hormonal disorder caused by increased production of growth hormone and insulin-like growth factor (IGF-1) in adulthood. A large majority of acromegaly cases are caused by a pituitary adenoma while a small percentage can be due to inherited genetic mutations that predispose to pituitary adenomas. Mutations in genes such as multiple endocrine neoplasia type 1 (*MEN1*), aryl hydrocarbon receptor-interacting protein (*AIP*) and G protein-coupled receptor 101 *(GPR101)* have been implicated (Yamamoto and Takahashi, 2022). The clinical features of acromegaly include gradual enlargement of the hands and feet. The facial features also change over time resulting in coarse facial appearance, thickening of the lips, enlarged nose, mandibular prognathism, and increased space between teeth (Fig. 1). In addition, acromegaly can cause enlargement of the internal organs like the heart, liver, and kidneys. Skin can become thickened, oily, and prone to sweating. Tongue and vocal cord swelling can lead to difficulty in speaking or swallowing and deepening of the voice. Acromegaly is associated with an increased risk of sleep apnea (Slagboom et al., 2023). Radiographic features include significant thickening of the cranial bones and enlargement of the frontal sinuses. Magnetic Resonance Imaging (MRI) of the pituitary gland is crucial for the diagnosis of acromegaly (Baptista et al., 2023).

### 6.2. Hyperparathyroidism and brown tumor

Primary Hyperparathyroidism (PHPT; OMIM #145000) is an autosomal dominant disorder of mineral metabolism manifesting as hypercalcemia due to excessive parathyroid hormone secretion (Simonds, 2017). Minor changes in the extracellular calcium concentration are detected by calcium sensing receptors (CaSRs). of parathyroid cells. Dysregulated overgrowth of parathyroid glands combined with reduced expression of CaSRs forms the fundamental pathophysiologic basis of PHTP. A genetic basis of PHPT can be seen in about 10 % of all cases (Minisola et al., 2022). Genetic form of PHPT can occur as part of Multiple Endocrine Neoplasia (MEN 1–4) syndromes (Minisola et al., 2022). Multiple genes have been implicated in both syndromic and

sporadic parathyroid tumorigenesis and related syndromes (Simonds, 2017). Secondary hyperparathyroidism can also manifest as excessive parathyroid hormone (PTH) secretion secondary to chronic renal failure. PTH plays major role in calcium and skeletal metabolism. Both hypocalcemia and hyperphosphatemia act as triggers for PTH secretion can be reduced by 1, 25, $(OH)_2$ Vitamin D, and hence decreased active vitamin D can also trigger PTH production. The increased PTH production causes increased calcium in the blood due to its influence on the bones, intestines, and kidneys. Prolonged stimulation of parathyroid gland results in parathyroid hyperplasia. Secondary hyperparathyroidism is also noted in Vitamin D-deficient rickets, malabsorption and pseudohypoparathyroidism (Muppidi et al., 2023). Brown tumor also called osteoclastoma is a common jaw manifestation of hyperparathyroidism. It presents with osteolysis and fibrosis due to excess osteoclastic activity. Increased vascularity, hemorrhage and hemosiderin deposition within the tumor imparts the brown color. The oral features of HPT relate to the effects of bone expansion which occur irrespective of whether or not brown tumor develops. The patients experience facial asymmetry, difficulty with speaking and mastication, malocclusion and tooth mobility. Some instances of structural tooth defects like enamel and dentin hypoplasia have been observed. The impact of bony expansion on the neurovascular canal within the jaws can result in bone pains and neuropathy (Palla et al., 2018).

### 6.3. Paget's disease

Paget disease of bone (osteitis deformans) (OMIM #167250) is a metabolic disorder commonly seen in individuals over 50 years of age. The basic pathophysiology is increased osteoclastic bone resorption, abnormal bone production and dysregulated bone turnover leading to abnormal bone expansion and deformities. Paget disease can be either monostotic or polyostotic. Germline mutations of different genes have been identified, particularly 30 germline mutations of the sequestosome 1 gene (*SQSTM1*) gene on chromosome 5q35 (Gennari et al., 2022). In addition, germline mutations of zinc finger protein 687 (*ZNF687)* and profilin 1 (*PFN1)* genes are known to be associated with severe, early-onset polyostotic Paget disease of bone (Gennari et al., 2022). Familial association has been demonstrated as well as an association with paramyxovirus based on occurrence of cytoplasmic and nuclear inclusions of virus in osteoclasts (Banaganapalli et al., 2023). Histologically, the severity of the disease correlates with frequency of intranuclear inclusions. The skull bones are affected in addition to the pelvis, cervical, thoracic, and lumbar bones of the vertebral column (Rai et al., 2016). Studies showed involvement of maxilla and mandible to be about 17 % with slight predilection for the maxilla relative to the mandible (Fig. 4). Many patients remain asymptomatic but those with symptoms may present with arthritis, bone pain, pathologic fractures, bowing of legs, kyphosis, hearing loss, enlargement of skull and facial bones, facial paralysis and even blindness. Radiography is the imaging modality of choice while bone scintigraphy can be used to monitor disease progression and response to treatment (Lombardi et al., 2022). Osteolytic lesions present with well-defined borders on radiographs. The radiographic changes are pronounced in the femur, pelvis, and skull. The mixed and late sclerotic phases of Paget disease show the classic radiographic features namely, cortical thickening, coarse trabecular pattern, bone marrow sclerosis and long bone deformities. Bisphosphonates are the drugs of choice for treatment (Lombardi et al., 2022).

### 6.4. Osteoporosis

Osteoporosis (OMIM #166710) is a common bone disorder characterized by low bone mineral density and structural deterioration of bone architecture predisposing patients to increased risk for fractures. Although it is more prevalent in postmenopausal women, men can also be affected. Genetic predisposition plays a role in determining an individual's susceptibility to osteoporosis. Several genes have been identified that have been associated with bone metabolism and thereby influence bone density. Osteoporosis is associated with various molecular changes in bone that contribute to the loss of bone mass and weakening of the bone structure. Some hormonal imbalances and key skeletal molecular changes affecting the interactions of receptor activator of NF-kappa-B and its ligand (RANK-RANKL) in osteoporosis result in dysregulated bone remodeling, increased osteoclast activity and decreased osteoblast activity. Chronic low-grade inflammation and inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) also promote osteoclast activity to further increase bone loss. Bone mineral density changes in osteoporosis can be observed in the dental panoramic radiographs and it has direct correlation with development of periodontal diseases. So, the early signs of osteoporosis may be picked up by the dental healthcare provider (Geurs et al., 2003). Guidelines for management of osteoporosis are well outlined and varies with the severity of estrogen deficiency and bone mass depletion.

## 7. Drug-induced craniofacial deformity

Medication-related osteonecrosis of the jaw (MRONJ) is characterized by bone devitalization and breakdown associated with use of antiresorptive drugs such as bisphosphonates and denosumab (Ruggiero et al., 2022). The necrotic bone may or may not be exposed to the oral cavity because the overlying oral soft tissue may be intact. However, inadvertent trauma, poor oral health or invasive dental procedure like tooth extraction and periodontal therapy can precipitate exposure of the necrotic bone to the oral cavity (Omolehinwa and Akintoye, 2016). It is still unclear why MRONJ occurs exclusively in the jaw despite several theories that have been proposed (Akintoye, 2014). According to the American Association of Oral and Maxillofacial Surgeon, MRONJ definition includes several key factors. First, is current or prior treatment with antiresorptives combined with or without immune modulators or antiangiogenic medication. Second is exposed jaw bone or bone that can be probed through an intra or extraoral fistulae in the jaws. Third, there should be no history of radiation therapy (Ruggiero et al., 2022). Recently, an association between antiangiogenic medication and MRONJ has been suggested (Srivastava et al., 2021). Although Raloxifene, a selective estrogen receptor modulator has fewer side effects relative to other antiresorptives, MRONJ has also been reported in some patients on Raloxifene (Bindakhil et al., 2021). Interestingly, fibrous dysplasia/McCune-Albright syndrome patients treated with antiresorptives seem to have low susceptibility to spontaneous MRONJ (Nadella et al., 2022).

## 8. Clinical and management implications of craniofacial disorders

A multidisciplinary approach to treatment is essential for management of patients with craniofacial disorders and dysplasia. This often involves the collaborative efforts of geneticists, radiologists, molecular biologists, surgical specialists, speech therapists and social service providers. Patients often have multiple orofacial and dental challenges and there is potential overlap of the syndromic conditions with other skeletal disorders. Pharmacological and surgical treatment of craniofacial bone and soft tissues may need to be combined with pharmacotherapy, speech therapy and physical therapy (Gangopadhyay et al., 2012).

Surgery is mostly advised to prevent neurodevelopmental delays and effects of elevated intracranial pressure in craniosynostosis (Marbate et al., 2022). Orthodontic treatment to correct occlusal issues and reconstruction of jaws, bone grafting, and distraction osteogenesis are recommended to enhance esthetics and improve function. Psychological counseling and treatment are an important part of the treatment planning for hemifacial microsomia (Lopez et al., 2022). There may be a need for supportive care to decrease complications, improve function and quality of life parameters,

## CRediT authorship contribution statement

**Sunday O. Akintoye:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Akinyele O. Adisa:** Writing – original draft, Data curation. **Chukwubuzor U. Okwuosa:** Writing – original draft, Data curation. **Mel Mupparapu:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation.

## Declaration of competing interest

None.
All authors have no conflict of interest to declare.

## Data availability

No data was used for the research described in the article.

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