Orodental abnormalities in limb malformation syndromes: a review article

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Received 06-Aug-2020
Revised 01-Oct-2020
Accepted 15-Oct-2020
Published 31-Dec-2020

Middle East Journal of Medical Genetics
2020,9:1–9*

The regular synchronization during development of an embryo results in the normal formation of his/her structures. The deviation from this harmony produces malformations. The pleiotropic effects of similar genes that contribute in the growth of limb and oral structures produce concurrent abnormalities indeed. The present review gives a brief hint at the shared causative genes of both limb and orodental structures. The nosology either of skeletal and limb malformations or of orodental findings and the types of orodental anomalies were reported in these syndromes. Pathognomonic orodental features and Egyptian experiences are emphasized.

Keywords:
gene mutations, limb malformations, oral anomalies

Middle East J Med Genet 9:1–9

Background

Birth defects are malformations programmed by gene mutations or by environmental insults such as infections and teratogens. The definition of congenital defects is structural or functional disabling disorder having physical, social, and intellectual influences (Feldkamp *et al*., 2017). The WHO declared that the prevalence of birth defects among neonates is one in 33 (Kurdi and Majeed-Saidan, 2015). An Egyptian study found that prevalence of congenital defects was 3.17% (Temtamy *et al*., 1998a, b), whereas another Egyptian study stated that congenital defects was 20 in 1000 neonates (Shawky *et al*., 2010a, b).

Congenital limb malformations follow congenital heart diseases as most frequent anomalies occurring in new-borns. Limb defects are exhibited either as an isolated entity or as a part of syndrome. Upper/lower or both extremities, unilateral or bilateral, are the affected sites in limb disorders (Tayel *et al*., 2005). Congenital limb defects have a percentage of 3.52% in fetal records; however, Egyptian percentage is ~8.8% (Shawky and Sadik, 2011; Shi *et al*., 2018). Increasingly, the high rate of positive consanguinity in Egypt as well as exposure to teratogenic environmental factors raises the limb malformations to ~20% among neonates when compared with other birth defects (Temtamy *et al*., 1998a, b).

The detailed clinical data should be accomplished by orodental examination. The full picture of the anomaly or syndrome characterization is usually associated with certain pathognomonic orodental findings, apart from its clinical description. This aids in accurate diagnosis, precise genetic counseling, correct treatment planning, and appropriate dental management if available.

The present review gives a brief hint on the developmental background and the shared causative genes of both limb and orodental structures. The nosology either of skeletal and limb malformations or of orodental findings and the types of orodental anomalies were reported in these syndromes. Pathognomonic orodental features and Egyptian experiences are emphasized.

Role of molecular genetics in the development of human limb and oral structures

Certain genes and their regulators are the maestro in the development of human limb and oral structures in a normal shape and function. T-Box transcription factors (*Tbx4-Tbx5*), the fibroblast growth factor genes (*FGF*s), the wingless inhibitory factor genes (*WNT*s), the sonic hedgehog genes (*SHH*), and the homeobox genes (*HOX*) and their formal interrelation directly regulate the embryological development of limb (Zuniga *et al*., 2012; Jin *et al*., 2019; Sun *et al*., 2019). Shh is a specific enhancer to regulate epithelium-mesenchymal proliferation,

which directly affects teeth, tongue, and palate. The sonic hedgehog signal coordinates WNT gene, which simultaneously influences tooth development (Sagai *et al*., 2017; Seo *et al*., 2018).

DLX genes have strategic influence on normal development of limbs (Kantaputra and Carlson, 2019). Moreover, distal-less genes (*DLXs*), *FGFs*, bone morphogenic protein (*BMP*), and homeobox are the principal genes involved in craniofacial growth and features' characterization (Richmond *et al*., 2018; Deshpande and Goudy, 2019). An informative review of molecular aspects of limb development is provided by Mundlos and Horn (2014). The identical timing in embryonic period which starts at fourth week of gestation and the similar shared genes involved in limb and oral structures formation make a possibility that the pathogenic gene variants could affect limbs, providing malformation as well as orodental anomalies.

Nosology and classification of limb malformation syndromes

One of the first classifications of limb malformations was established by Temtamy (1966) and published by Temtamy and McKusick in 1969. The classification was based mainly on clinical, anatomical, and genetic criteria. They divided the limb abnormalities into ten main groups (Table 1).

Each of the aforementioned 10 groups was classified anatomically as preaxial, mesoaxial, or postaxial; clinically as isolated or associated with other organ malformation; genetically as inherited or sporadic; and according to the pattern of inheritance (Temtamy 1966).

A nosology for skeletal disorders including limb anomalies was set in 1992 by Beighton *et al*. (1992) and updated regularly. Under the latest nosology classification skeletal disorders were included under 42 groups according to phenotypic presentations and protein nomenclatures (Table 2) (Mortier *et al*., 2019).

Orodental abnormalities associated with limb malformation syndromes

The known limb malformation syndromes associated with significant orodental findings are included in Online Mendelian In Man (OMIM) and London Dysmorphology Databases (Winter and Baraitser, 2014).

Certain orodental features are commonly observed in most disorders, whereas a pathognomonic phenotype should be highlighted for helping in accurate diagnosis.

Upon discussing the Filamin group in the latest Nosology (2019), otopalatodigital syndrome (OMIM# 304120) is considered a disorder of syndactyly in hands and toes, clinodactyly of fifth fingers, short first metacarpal, and absent fibula. Characteristic features in the ears are conductive deafness and poorly modeled pinnae (Winter and Baraitser, 2014) The ultimately oral characterization of the syndrome is cleft palate, as well as bifid uvula and marked micrognathia (Robertson, 2007). The ciliopathies group includes chondroectodermal dysplasia (Ellis-Van Creveld syndrome (OMIM#225500), orofaciodigital syndrome (OMIM#311200, 252100), and short-rib- polydactyly syndrome (OMIM#613091), which are described with polydactyly of fingers or toes; moreover, absent fibula and syndactyly was reported with short-rib syndrome. These disorders shared similar orodental features (Table 3).

When mentioning the acromelic group, trichorhinophalangeal syndrome (OMIM#190350, 150230), characterized by brachydactyly, short feet, and wide hallux disorders, has noticeable oral anomalies, including micrognathia, accentuated obtuse angle of the mandible, supernumerary teeth, and malocclusion (Candamourty *et al*., 2012; Trippella *et al*., 2018). Less significant facial abnormalities are long flat philtrum, thin upper lip, and cleft palate (Trippella *et al*., 2018; Cho *et al*., 2019).

Robinow syndrome (OMIM#180700, 268310) was placed under the mesomelic/rhizomelic dysplasia group; it is also considered one of the brachydactyly syndromes. The dominant type has tented upper lip, long philtrum, and retromicrognathia. Intraoral examination revealed remarkable findings of gingival overgrowth, bifid uvula or palatal cleft, tongue ankyloglossia that leads to bifid tip of the tongue, malpositioned crowding teeth, and congenital teeth agenesis (Temtamy *et al*., 2004a, 2004b; Beiraghi *et al*., 2011). Campomelic dysplasia (OMIM#114290) presents with short metacarpals, brachydactyly, and clinodactyly of fifth

Table 1 Classification of limb malformations according to Temtamy and McKusick (1969)

The different groups of limb malformations		
I-Absence deformities	II-Brachydactyly	III-Syndactyly
IV-Polydactyly	V-Contracture deformities of the digits	VI-Arachnodactyly
VII-Symphalangism	VIII-Carpal/Tarsal synostosis	IX-Macrodactyly

X-Syndromes with miscellaneous hand malformations.

Table 2 The latest nosology classification of skeletal malformation disorders (Mortier *et al.*, 2019)

Groups			
1-FGFR3 chondrodysplasia group	2-Type 2 collagen group	3-Type 11 collagen group	4-Sulphation disorders group
5-Perlecan group	6-Aggregan group	7- Filamin group and related disorder	8-TRPV4 group
9-Ciliopathies with major skeletal involvement	10-Multiple epiphyseal dysplasia and pseudoachondroplasia group	11-Metaphyseal dysplasia	12-Spondylometaphyseal dysplasia
13-Spondyloepimetaphyseal dysplasia	14-Severe spondylodysplastic dysplasia	15-Acromelic dysplasia	16-Acromesomelic dysplasia
17-Mesomelic and Rhizomelic dysplasia	18-Bent bone dysplasia	19-Primordial dwarfism and slender bone group	20-Dysplasia with multiple joint dislocations
21-Chondrodysplasia punctate	22-Neonatal osteosclerotic dysplasia	23-Osteopetrosis and related disorders	24-Other sclerosing bone disorders
25-Osteogenesis imperfecta and decrease bone density group	26-Abnormal mineralization group	27-Lysosomal storage diseases with skeletal involvement	28-Osteolysis group
29-Disorganized development of skeletal component group	30-Overgrowth (Tall stature) syndromes with skeletal involvement	31-Genetic inflammatory/ Rheumatoid-like osteoarthropathies	32-Cleidocranial dysplasia and related disorders
33-Craniosynososis syndromes	34-Dysostosis with predominant craniofacial involvement	35- Dysostosis with predominant vertebral with and without costal involvement	36-Patellar dysostoses
37-Brachydactylies without extra-skeletal manifestations	38-Brachydactylies with extra-skeletal manifestations	39-Limb hypoplasia- reduction defects group	40-Ectrodactyly with or without other manifestations
41-Polydactyly-Syndactyly-Triphalangism group	42-Defects in joint formation and synostosis		

Table 3 Main pathognomonic orodental abnormalities exhibited in the group of ciliopathies with limb malformations

	Syndrome		
Orodental anomalies	Ellis-Van Creveld (Mostafa *et al.*, 2005)	Orofaciodigital (Adyanthaya and Adyanthaya, 2015)	Short-rib-polydactyly (Badiner *et al.*, 2017)
Natal teeth	+	-	+
Clefted alveolar ridge	+	+	+
Multiple labial frenum	+	+	+
Hypodontia	+	+	+
Lobulated tongue	–	+	–
Bifid tip of the tongue	+	+	–
Partial ankyloglossia	+	+	–
Notched upper lip	+	–	+
Abnormal shaped teeth	+	+	–
Tight vestibule	+	+	–
Cleft lip/palate	–	+	+
Furrowed tongue	+	+	+
Micrognathia	–	+	–

fingers. The distinctive intraoral structures of the syndrome are microstomia, long philtrum, cleft palate, and retromicrognathia (Corbani *et al.*, 2011).

Desbuquois dysplasia (OMIM#251450) was listed under the dysplasia with multiple joint dislocations group. It is characterized by progressive ossification of second metacarpals, bifid distal phalanx of the thumb as well as, dislodgment of interphalangeal joints. Microstomia and small retruded mandible are the only reported oral abnormalities of the disorder (Laccone *et al.*, 2011).

The group of other sclerosing bone disorders included oculodentoosseous dysplasia (OMIM#164200, 257850), also known as oculodentodigital. This dysplasia is characterized by syndactyly and clinodactyly. Dental abnormalities are very specific and diagnostic, including enamel hypoplasia, odontodysplasia, microdontia, delayed teeth eruption, and hypodontia (Aminabadi *et al.*, 2010).

The osteolysis group includes Hajdu-Cheney syndrome (OMIM#102500) and multicentric carpal-tarsal osteolysis syndrome (OMIM#166300). Both disorders shared acroosteolysis phenomena of carpal and tarsal bones with deformities of digits. Micrognathia is the main oral anomaly observed in the osteolysis group (Samuel *et al.*, 2016; Choochuen *et al.*, 2018), as well as premature loss of teeth, which is diagnostic in Hajdu-Cheney syndrome (Samuel *et al.*, 2016).

The overgrowth syndromes with skeletal involvement group contained five disorders; two of them are characterized by arachnodactyly and

camptodactyly, namely, the congenital contractural arachnodactyly (OMIM#121050) and Marfan syndrome (OMIM#154700). They share similar oral manifestations except few features that are presented in Table 4 (Marina *et al.*, 2003; Bollero *et al.*, 2017). Another disorder not included in the nosology owing to it is rarity is van den Ende-Gupta syndrome (OMIM#600920). It is one of the contractural and arachnodactyly disorders. The only two oral anomalies reported were maxillary hypoplasia and everted lower lip (Schweitzer *et al.*, 2003).

The remaining two disorders under the overgrowth group that have macrodactyly according to Temtamy's classification are Proteus syndrome (OMIM#176920) characterized by facial asymmetry, premature eruption of teeth, and large jaws of the affected side, as well as malocclusion, and enamel hypoplasia (Canabarro *et al.*, 2008). Sotos syndrome (OMIM# 117550) was also in the group of macrodactyly in the old nosology (Temtamy and McKusick, 1978). Oral examination includes premature eruption of teeth, high-arched palate, malocclusion, and hypodontia (Hirai *et al.*, 2011).

Hyaline fibromatosis syndrome (OMIM#228600) is under the group of genetic inflammatory/ rheumatoid-like osteoarthropathies. The joints and digits show contractures with deformities in knees and elbows, resulting in limbs' movement limitation. Orally, it presents by gingival fibromatosis which aids in the diagnosis (Olczak-Kowalczyk *et al.*, 2011).

Two syndromes belonging to the craniosynostosis group are presented with syndactyly, Apert syndrome (OMIM#101200) and Saethre-Chotzen syndrome (OMIM#101400), whereas a third one has radial aplasia and absent thumbs, which is the Baller-Gerold syndrome (OMIM#218600). The first exhibited bifid uvula, Byzantine pseudocleft at the anterior area, and malocclusion (Şoancă *et al.*, 2010). The second showed mainly high-arched palate, hypoplastic maxilla, and protruded mandible (Pelc and Mikulewicz, 2018). The last displayed palatal abnormalities bifid uvula, cleft or high-arched palate, and micrognathia (Murthy *et al.*, 2008).

Table 4 Oral manifestations associated with congenital contractural arachnodactyly and Marfan syndrome

Anomaly	Congenital contracture arachnodactyly (Marina *et al.*, 2003)	Marfan (Bollero *et al.*, 2017)
High-arched palate	+	+
Cleft palate	+	+
Anterior open bite	+	+
Spindly roots	+	+
Enamel hypoplasia	+	+
TMJ disorders	–	+
Dental occlusion	Spacing	Crowding
Prognathism	Rarely	Sometimes
Micrognathia	Often	Rarely

An important group was classified in the latest nosology named dysostosis with predominant craniofacial involvement, which included four disorders: acrofacial dysostosis (Nager type) (OMIM#154400), which was first identified as a distinct syndrome by Temtamy and McKusick (1978); hemifacial microsomia (OMIM#164210), acromelic frontonasal dysostosis (OMIM#603671), and Weyers acrofacial dysostosis. The first 2 syndromes present with preaxial reduction defects, e.g., absent thumbs or radial aplasia, while the third one has tibial aplasia, talipes deformity, and polydactyly. The most characteristic facial feature is facial asymmetry, whereas oral anomalies comprise cleft palate, retromicrognathia, malocclusion, and temporomandibular joint ankylosis/ abnormalities (Martelli *et al.*, 2010; Ismail *et al.*, 2017). Acromelic frontonasal dysostosis presents with clefting and teeth agenesis (Koçak and Ceylaner, 2009). Weyers acrofacial dysostosis (OMIM#193530) has remarkable polydactyly and acroosteolysis. It is phenotypically similar to Ellis-Van Creveld syndrome except for additional amelogenesis imperfecta, which could be a diagnostic finding, in addition to its autosomal dominant pattern of inheritance (Shetty *et al.*, 2012).

Brachydactilies with extra-skeletal manifestations provisionally consist of Rubinstein-Taybi syndrome (OMIM#180849), Temtamy preaxial brachydactyly syndrome (OMIM#605282), Coffin-Siris syndrome (OMIM#135900), and pseudohypoparathyroidism (OMIM#103580). Talon cusp dental malformation is helpful in the diagnosis of Rubinstein-Taybi and Temtamy syndrome (Temtamy *et al.*, 1998a, b; Gunashekhar, Hameed and Bokhari, 2012). Microdontia and retromicrognathia are cliché for Coffin-Siris (Hoyer *et al.*, 2012), whereas enamel hypoplasia, microdontia, delayed eruption, and short roots are the obvious dental findings in pseudohypoparathyroidism (Hejlesen *et al.*, 2018).

The many syndromes in limb hypoplasia/reduction defects group are Hanhart syndrome (OMIM#103300), Moebius syndrome (OMIM#157900), Thrombocytopenia-Absent radius (TAR) (OMIM#274000), de Lange syndrome (OMIM#122470), and Roberts syndrome (OMIM#268300). The main oral feature observed in the five syndromes is palatal cleft. Tongue abnormalities such as hypoglossia, tongue asymmetry, or glossoptosis are marked in all disorders except TAR and Roberts syndromes. Micrognathia is fundamentally detected except in TAR (Naseh *et al.*, 2012; Leanza, Rubbino and Leanza, 2014; Ismail *et al.*, 2016; Hassib *et al.*, 2019;

Varal and Dogan, 2019). The group of ectrodactyly with or without other manifestations contains ectrodactyly-ectodermal dysplasia-cleft lip/palate (EEC) (OMIM#604292), ankyloblepharon-cleft lip/palate (AEC, Hay-Wells, Rap-Hodgkin) (OMIM#106260), and limb-mammary syndrome (OMIM#603543). Split hand/foot malformations, a combination of central ray reduction defects and syndactyly, are the cardinal limb malformations. The lip/palate clefting is the principal oral anomaly found in the syndromes, whereas limb-mammary disorder has hypodontia as the main dental abnormality (Van Bokhoven *et al.*, 1999; Koul *et al.*, 2014).

The last group of the latest skeletal dysplasia nosology includes other limb malformations as polydactyly-syndactyly-triphalangism group, for example, Cenani-Lenz syndrome (OMIM#212780) and Lacrimo-auriculo-dento-digital syndrome (LADD) (OMIM# 149730). Both disorders have syndactyly, whereas triphalangism is only reported in LADD syndrome. Micrognathia is frequently observed in Cenani-Lenz syndrome (Hettiaracchchi *et al.*, 2018). Prominent dental anomalies in LADD are hypodontia, microdontia, and enamel hypoplasia (Talebi *et al.*, 2017).

It is worth noting that in the nosology of skeletal dysplasias list, many syndromes with limb malformations associated with orodental anomalies were not included, which gives a hint that this classification is still incomplete. The classification of limb malformations by Temtamy and McKusick (1978) included the contracture and camptodactyly group, for example, Bartoscas-Papas syndrome (OMIM#263650), which is a lethal condition associated with cleft of the lip/palate and synechia (Kalay *et al.*, 2012); Freeman-Sheldon syndrome (OMIM#193700), which presents with markedly long philtrum, microstomia, microglossia, high narrow palate and limited movement of soft palate (Johns, 2013); Gordon syndrome (OMIM# 114300), which exhibits cleft palate and micrognathia (Alisch *et al.*, 2016); and Trismus pseudocamptodactyly (OMIM#158300), described by limited mouth opening is the crucial finding (Sreenivasan *et al.*, 2013).

Brachydactyly syndromes like Aarskog (OMIM#100050) shows maxillary hypoplasia, high-arched palate, and tooth agenesis (Ahmed *et al.*, 2016). The preaxial reduction defect syndrome of Juberg-Hayward (cleft lip/palate-abnormal thumb and microcephaly) (OMIM#216100) is only associated with clefting (Silengo and Tornetta, 2000). Syndactyly and polydactyly group presented by focal dermal hypoplasia (OMIM#305600), which orally has gingival papillomas, hypodontia, microdontia, and enamel hypoplasia (Nathwani *et al.*, 2018).

Egyptian experiences concerning orodental abnormalities associated with limb malformation syndromes

Temtamy *et al.* (1989), studied orodental and ultrastructural changes of pulp and gingiva in Marfan syndrome. The results revealed gingivitis and periodontitis in Marfan patients as a consequence of the increase of elastic fibrous tissue and defective collagen fibers. Orodental findings exhibited high-arched palate, enamel hypoplasia, and malocclusion. The pulp showed pulp stone and obliterated root canals with abnormal root morphology.

Rubinstein-Taybi syndrome was studied by Temtamy *et al.* (1990) and Shawky *et al.* (2012) who presented the clinical, facial, and orodental phenotype of the syndrome among Egyptians. Talon cusps were prominent findings of the conditions shown by Temtamy *et al.* (1990).

Ectrodactyly-ectodermal dysplasia-cleft lip/palate was studied by Meguid *et al.* (1995) and Ashour and El-Badry (2004) who presented the variability in phenotypic characterization of the syndrome. Hypodontia, microdontia, enamel hypoplasia as well as cleft palate were the predominating features.

Temtamy *et al.* (1998a, b) first described the Temtamy preaxial brachydactyly syndrome characterized by multiple congenital anomalies and preaxial brachydactyly. Oral examination showed micrognathia, high-arched palate, microdontia, and talon cusps. Temtamy *et al.* (2012) studied the largest series of Temtamy preaxial brachydactyly syndrome with main digital and orodental anomalies (Temtamy *et al.*, 2012). Aglan *et al.* (2014) reported a novel gene mutation in an additional Egyptian case with the same disorder suffering of same facial and orodental involvement.

Temtamy *et al.* (2003a, b, c) reported two families with Cenani-Lenz syndrome emphasizing for the first time in the literature the associated facial dysmorphism and orodental features including short prominent philtrum and malar hypoplasia.

The phenotypic spectrum of Baller-Gerold syndrome was investigated in details by Temtamy *et al.* (2003a, b, c). Orodental malformations were bifid uvula, cleft or high-arched palate, and micrognathia.

Orofaciodigital syndrome one of the polydactyly group of disorders was reported by Temtamy

et al. (2003a, b, c) and Shawky *et al.* (2013; 2014). All reported the phenotypic variability of the syndrome. Multiple frena, clefted alveolar ridge, and lobulated tongue nodules were vigorously observed.

A genetic study of 46 Egyptian patients with congenital limb contractures was performed by Temtamy *et al.* (2004a, b). The authors provided full clinical and orodental studies to different contracture syndromes

Gingival overgrowth, delayed tooth eruption, tie tongue, and bifid tip of the tongue were the main orodental anomalies reported in Robinow syndrome by Tematamy *et al.* (2004). Histopathological studies revealed storage material in the gingiva. Aglan *et al.* (2015) reported four novel gene mutations in Robinow syndrome without altering the oral phenotype. One patient received surgical management to correct lip, nose, and zygomatic bone hypoplasia (Mossaad *et al.*, 2018).

Ellis-Van Creveld syndrome was very challenging in orodental description, as the mentioned features were primarily reported by Mostafa *et al.* (2005). Orodental anomalies in this disorder are similar to those in the oro-facio-digital syndrome group except for the tongue nodules. Shawky *et al.* (2010a, 2010b) found extrafacial dysmorphism in another Egyptian case that presented with corneal abnormality, upward slanting palpebral fissures, and frontal bossing. A doctorate thesis was provided applying overdenture to restore the tooth agenesis in the anterior area associated with this disorder (AbdelKader, 2015). The study concluded that the ball/socket-retained partial overdenture was better than bar/clip-retained overdenture in terms of stress distribution.

Roberts syndrome which is characterized by phocomelia and cleft lip/palate was first delineated by Temtamy (1966), and Temtamy *et al.*, 2006. Afifi *et al.* (2016) found new hypopigmentation in Roberts cases with a novel mutation. Genotype/phenotype correlation was studied in eight patients by Ismail *et al.* (2016).

Mehrez *et al.* (2010) provided the first cephalometric measurements to assess craniofacial involvement in some reduction defect syndromes. They proved the existence of cranio-facial and orodental abnormalities related to such category of disorders.

Abdalla (2016) described the clinical and radiographic findings in a case of Nager acrofacial dysostosis. The clinical, radiographic, and orodental examination confirmed the diagnosis. Ismail *et al.* (2017) detected a novel mutation and classical clinical and orodental features in the form of temporomandibular joint ankylosis, facial asymmetry, and retromicrognathia in another patient.

One case of Moebius syndrome was presented by Shawky (2015) who observed orofacial and skeletal malformations. Four cases of Moebius syndrome were published by Hassib *et al.* (2019). The cases had tongue abnormalities, retromicrognathia, enamel hypoplasia, and malocclusion. Ridge asymmetry was a new finding not previously reported. A modified prosthetic management was provided to one affected patient.

Demographic studies among certain Egyptian governorates were performed to calculate the prevalence of limb malformations and orofacial clefts among the country. Shawky *et al.* (2010a, b) examined 140 patients in Cairo, and syndromic limb anomalies were 54.6% of the total affected individuals. A wider study done by Shawky and Sadik (2011) included ~660 000 patients from all over Egypt. They concluded that limb malformations and clefting of palate/lip among congenital anomalies were 8.8 and 1.5%, respectively. On studying Assiut governorate patients, Mohammed *et al.* (2011) found that skeletal abnormalities were 37.9% and cleft lip/palate were 9.7. Abulezz *et al.* (2016) surveyed hand malformations in Upper Egypt. Syndactyly and polydactyly were of high percentages, with 36 and 27, respectively. In Menoufia Governorate, AbouEl-Ella *et al.* (2018) found that skeletal anomalies and cleft palate/lip were 48 and 6%, respectively, whereas in Alexandria, Abdou *et al.* (2019) reported that musculoskeletal abnormalities were 32.9% and other anomalies were 4.2%, which may include orofacial clefting.

This review has shown that the pleiotropic effects of genes participating in limb and oral structure development may explain the simultaneous malformations occurring during the embryonic period. Despite the large number of publications concerning limb anomalies in association with orodental abnormalities, new findings are still noticed which could help in determining the stereotype of the syndrome and delineate its phenotypic spectrum. Genotype/phenotype correlation is not yet well defined in most of the mentioned syndromes, especially craniofacial descriptions, which need further studies. Some syndromes remain very rare worldwide; thus, reaching the correct diagnosis in combination with orodental descriptions is a scientific precedent. The conjunction of clinical and orodental examination is of ultimate importance for the diagnostic accuracy and the genetic counseling. Although, oro-dental anomalies are associated with many syndromes, the oro-dental geneticists are few in number, and this domain is still not well propagated worldwide. The

pathogenesis of various oral and dental developmental abnormalities, as well as their causative genes remains mostly unknown.

Acknowledgements

Nehal F. Hassib contributed in collection of data, writing of the manuscript, and manuscript submission; Eman A. AbulEzz contributed in revision of the orodental part; Magda Ramzy contributed in editing of the manuscript; Tarek El-Badry contributed in editing of the manuscript; Mona S. Aglan contributed in correcting the clinical part of the manuscript; and Samia A. Temtamy contributed in revision and editing of the whole manuscript and providing many of the reference list.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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