Review

The genetic basis of inherited anomalies of the teeth.
Part 2: Syndromes with significant dental involvement

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Abstract

Teeth are specialized structural components of the craniofacial skeleton. Developmental defects occur either alone or in combination with other birth defects. In this paper, we review the dental anomalies in several multiple congenital anomaly (MCA) syndromes, in which the dental component is pivotal in the recognition of the phenotype and/or the molecular basis of the disorder is known. We will consider successively syndromic forms of amelogenesis imperfecta or enamel defects, dentinogenesis imperfecta (i.e. osteogenesis imperfecta) and other dentine anomalies. Focusing on dental aspects, we will review a selection of MCA syndromes associated with teeth number and/or shape anomalies. A better knowledge of the dental phenotype may contribute to an earlier diagnosis of some MCA syndromes involving teeth anomalies. They may serve as a diagnostic indicator or help confirm a syndrome diagnosis.

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1. Introduction

Dental anomalies, even when minor, have been reported as significant components of many syndromes. Their presence may be a valuable diagnostic clue in the identification of specific patterns of developmental disturbance. Teeth abnormalities may serve as a diagnostic indicator or help confirm a syndromic diagnosis. The Winter—Baraitser Database v 1.0.12 (previously: London Dysmorphology Database — LDDB) references 793 entities with abnormal teeth, among which 147 have abnormally shaped teeth, 219 oligodontia, 28 dentin and 128 enamel anomalies. A closer look at the relevant entries demonstrates that, in most situations, the exact dental anomalies are poorly or even inadequately described, or concern a minority of cases.

For didactic reasons, isolated abnormalities of the shape and/or structure of the teeth were distinguished from the abnormalities of number associated with multiple congenital anomalies (MCAs). This oversimplification should not hide the fact that, in some instances, a mutation in a gene involved in MCA can also be reported as an isolated dental symptom.

In this paper, we will focus on the most important and most characteristic disorders. The reader will find additional data on other syndromes in Tables I—X (Supplementary Material 1). All the loci of the syndromes presented in these reviews are summarized in appendix 1 (Supplementary Material 1).

2. Syndromes associated with amelogenesis imperfecta (AI) and enamel hypoplasia

Although usually isolated, AI is a component of several MCAs (Supplementary Material 1, Table I). Constitutional enamel anomalies must be considered cautiously as they can easily be misdiagnosed, when they are secondary to metabolic or environmental factors (including extensive decay…), as shown in a review of oro-dental defects in the Prader—Willi syndrome [5].

2.1. Tricho-dento-osseous syndrome

The tricho-dento-osseous syndrome (TDO, OMIM 190320) is characterized by kinky, coarse and/or curly, fair coloured hair, present at birth in 80% of cases. Half of the patients retain this phenotype beyond infancy. More than 90% of individuals with TDO have an increased cranial thickness, obliterated diploë and absence of mastoid pneumatization [156]. Teeth show uniformly thin or pitted hard enamel, enlarged pulp chambers, and taurodontism. The degree of taurodontism and the distribution of affected teeth are highly variable. In some individuals there is severe taurodontism of all the posterior teeth while the anterior teeth show only enlarged pulp chambers. Both primary and permanent teeth are typically affected [61]. Dental anomalies in TDO are similar to those observed in AI hypomaturation—hypoplasia type with taurodontism (AIHHT, OMIM 104510), which is inherited as a highly penetrant autosomal dominant trait. AIHHT shows no alterations in hair or bone.

A common four base pair deletion in exon 3 of the human DLX3 gene located on human chromosome 17q21.3—q22 [132] has been identified in TDO families [121]. Although the dental findings of the AIHHT are similar to those of TDO, AIHHT is a distinct condition, usually not linked to DLX3 [122]. Nevertheless, Dong et al. [35] identified a deletion of two nucleotides in the homeodomain of the DLX3 gene in a large AIHHT pedigree, suggesting that some forms of AIHHT are allelic to TDO. The clinical pattern of expression of DLX3 mutations depends on the altered functional domain of the DLX3 protein: AI and taurodontism are a constant feature but hair and bone anomalies are observed with mutations outside the homeodomain [121].
Interestingly, the expression of DLX3 transcription factor was shown to be related to matrix synthesis and biomineralisation in all skeletal tissues [44].

2.2. Cone—rod dystrophy and amelogenesis imperfecta

The association of cone—rod dystrophy with AI (OMIM 217080) has only been reported twice, in a large consanguineous Arabic family [62] and in a two-generation family from Kosovo [99]. Individuals present in the first few years of life with photophobia, horizontal nystagmus, and reduced central vision. Inability to see clearly in bright light (hemeralopia) is reported by the end of the first decade. The progressive cone—rod dystrophy is associated with hypoplastic/hypomineralized AI. Teeth are dysplastic, yellow/brown, with almost no visible enamel [99]. By linkage analysis in the first family Downey et al. [36] identified a locus on chromosome 2q11.

2.3. Kohlschütter—Tönz syndrome

Kohlschütter—Tönz syndrome (OMIM 226750) is a neuro-degenerative condition consisting of hypomineralized AI (with yellow teeth), seizures, progressive spasticity, ataxia and often psychomotor regression. Onset is between 1 and 2 years and death occurs in childhood or adulthood. Additional manifestations variably include myopia, cardiac ventricular enlargement, cerebellar vermis hypoplasia, dry skin, and broad thumbs/toes [27,163,158,49]. Data are consistent with AR inheritance. It has been hypothesized that heterozygotes may express AI without neurological impairment [48].

2.4. AI with nephrocalcinosis (McGibbon syndrome)

AI with nephrocalcinosis (OMIM 204690) is rare and possibly underdiagnosed [89,83,50,31,109,117,57]. The common characteristics are the presence of thin or absent enamel (AI, hypoplastic type), intrapulpal calcifications, calculus, delayed tooth eruption, gingival hypertrophy, bilateral nephrocalcinosis and normal plasma calcium (Fig. 1). Impaired renal function is variable, or delayed to adulthood, despite the presence of typical renal hypechoegenicity in childhood. McGibbon syndrome has been previously reported in consanguineous and non-consanguineous families. Actually, the relationship between the enamel defect and nephrocalcinosis is still unknown. Kidney ultrasound scan should be performed in all AI patients in order to exclude nephrocalcinosis and to determine if this alteration is exclusive to this rare syndrome or can be found in other forms of AI [117,57].

Suda et al. [145] reported a patient exhibiting AI, hypomaturation type, and bilateral cleft lip and palate, nephrocalcinosis and hematuria at the age of 15 years. These symptoms appeared to be secondary to polycystic kidney disease. Based on a phenotypic homology with a mouse model, the authors screened MSX2 and found a missense mutation (T447C) in this patient. MSX2 (HOX8) gain-of-function mutations are associated with dominant craniosynostosis, Boston type. The same point mutation has been identified in 10% of patients with non-syndromic sagittal craniosynostosis.

2.5. Vitamin D-dependent rickets

Vitamin D-dependent rickets, type I (VDDRI, OMIM 264700) is an AR defect in vitamin D metabolism. Patients with VDDRI have mutations of the 1-alpha-hydroxylase gene (located at
12q13.1–q13.3) resulting in decreased levels of 1,25(OH)2 vitamin D3 [74]. Clinical features include growth failure, hypotonia, rachitic bones and enamel hypoplasia. Zambrano et al. [159] described a patient with hypoplastic, yellow-to-brownish enamel on all permanent teeth, and periodontal disease. Dental radiographs showed large quadrangular pulp chambers and short roots. Ultrastructural examination showed anomalies affecting both enamel and dentin.

2.6. Vitamin D-resistant rickets

Mutations in the vitamin D receptor gene (12q12–q14) cause vitamin D-resistant rickets, type II (VDDR II, OMIM 277440). The circulating levels of 1,25-(OH)2 D3 are increased. Most patients have total alopecia. Bailleul-Forestier et al. [4] showed that 1,25-dihydroxyvitamin D3 controls different stages of tooth crown development in humans. Several genes involved in amelogenesis imperfecta are controlled by vitamin D [116].

2.7. Autoimmune polyendocrinopathy

Autoimmune polyglandular syndromes (APS) are characterized by multiple endocrine insufficiencies. APS type 1 (APS 1), also known as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED, OMIM 240300) or Whitaker syndrome, is an AR disorder characterized by chronic mucocutaneous candidiasis, multiple autoimmune endocrinopathies

![Fig. 1. Amelogenesis imperfecta with nephrocalcinosis. (A) Oral view teeth with hypoplastic enamel and calculus, (B) renal ultrasonography: medullary calcinosis with hyperechoic foci in the pyramids (arrow).](image)
hypoparathyroidism, adrenocortical failure, type 1 diabetes...) and ectodermal anomalies (vitiligo, alopecia, dysplastic enamel...) [118]. Onset is in childhood. APECED is due to mutations of the AIRE (autoimmune regulator) gene, located on chromosome 21q22.3. There is partial defect of the cell-mediated immunity (resulting in chronic skin candidiasis), and ectodermal dysplasia. The most frequent abnormality is enamel hypoplasia of permanent teeth, which affects 75% of the patients [86,119]. Enamel hypoplasia can be the first sign of APECED, and oral examination could help establish a diagnosis (Fig. 2).

3. Syndromic forms of dentinogenesis imperfecta

Dentinogenesis imperfecta (DGI) and dentin dysplasia are reported in many syndromes (Tables II–V summarize other syndromes involving dentin anomalies, see Supplementary Material 1). We have limited our review to the most significant disorders, selected because their molecular basis is known, or because the dental anomaly is the usual key feature.

3.1. Syndromes associated with DGI with a collagen mutation

3.1.1. DGI in osteogenesis imperfecta

Ninety percent of the dentin matrix is made of collagen, mostly type I, but also to a smaller extent types III and VII (www.bite-it.helsinki.fi). Dominantly inherited osteogenesis imperfecta (OI) results from mutations in COL1A1 (17q21) and COL1A2 (7q21.1), which encode the two chains of type I collagen. The association of DGI with OI is well known (cf. DGI type I in Shield classification, [140]). OI is commonly subdivided into several types based on clinical features, radiological criteria and the presence of DGI [77,142] (Supplementary Material 1, Table II). The prevalence of DGI in the primary dentition varies from 28% to 80% [87,111]. It is highest in OI types IIIB, and IVB [85,87,111], whereas it is rarer in OI type I. In OI type II — perinatal lethal, dental abnormalities may or may not be present [138,78,155]. Except when a parent is a mosaic, there is a very high concordance for the presence of DGI between affected parents and children, and between affected siblings [93]. Dental abnormalities, when present in a family, may be very helpful for early diagnosis of patients with mild bone fragility.
Patients with no signs of DGI at visual inspection can present with radiographic and/or histological evidence of this disorder [88]. This can explain why DGI is underdiagnosed in OI patients [153].

The dental phenotype of OI consists of greyish or brownish discoloration of the teeth and fracture of the enamel cap with secondary attrition [82] (Fig. 3A). The phenotype may vary between the primary and permanent dentition, and between teeth within a single dentition. O’Connell and Marini did not find a correlation with the nature of the mutation [111]. Tooth discoloration and attrition are less severe in the permanent dentition than in the primary one. In a study of 40 children, O’Connell and Marini were unable to distinguish OI type III from OI type IV by dental evaluation [111]. Radiographic anomalies of teeth include increased constriction at the corono-radicular junction, progressive obliteration of the pulp by secondary dentin, and roots thinner and shorter than normal (Fig. 3B). In OI type I, an oval pulp chamber with apical extensions into the coronal portions of the root has been reported [80]. These dental abnormalities are similar to those found in dentin dysplasia type II. In addition a well-circumscribed radiolucency involving the apices of all permanent mandibular incisors is observed in some patients [79,80,85]. The frequency of teeth with denticles is higher in OI patients type III and IV [87]. Malmgren and Lindskog [94] suggested that dysplastic changes in dentin are most likely an expression of genetic disturbances associated with OI and should not be diagnosed as DGI. Other tooth anomalies include transverse bands of discoloration of crowns, crown translucency, ectopic eruption or impaction of permanent molars, and dental agenesis [93]. In all types of OI, class III malocclusion, anterior and posterior cross-bites and open bites are commonly seen [111].

Fig. 3. Dentinogenesis imperfecta in osteogenesis imperfecta. (A) Oral view grey brown primary teeth and (B) orthopantomogram.
More than 150 different mutations have been reported in **COL1A1** (www.le.ac.uk/genetics/collagen/colla1.html), 21 of them (in OI type I, III and IV) with the DGI-I phenotype (Supplementary Material 2, Table I). In OI type 1, the presence of DGI is correlated with mutations leading to the synthesis of abnormal procollagen fibres, as opposed to decreased synthesis of normal collagen [19]. In the **COL1A2** gene, 17 mutations, were reported mostly associated with DGI (Supplementary Material 2, Table II). Mundlos et al. [103] described two large exon deletions in the triple helical domain of the **COL1A2** gene which present with different phenotypes: DGI or DD.

Some linkage studies [41] failed to distinguish between the OI type I and OI type IV, with or without DGI, suggesting that these two clinical phenotypes may result from different mutations of the pro alpha 2(I) chains. The finding that a mutation in the gene for the alpha 2(I) collagen chain with serious consequences for bone development has only minor effects in teeth suggests that odontoblasts, unlike osteoblasts, can largely compensate for this particular genetic defect, possibly by excluding the abnormal alpha 2(I) chains and forming alpha 1(I) homotrimeric collagen I which is expressed normally during initial dentinogenesis. The discrepant consequences in deciduous as opposed to permanent teeth and the specific localization of the dentin abnormalities in permanent teeth led Luder et al. to speculate that the exclusion of defective alpha 2(I) chains could depend on the developmental stage and/or the rate of extracellular matrix formation [84]. **COL1A1**, **COL1A2** and **DSPP** gene mutations can have a similar dental phenotype. Scriver et al. [135] proposed that mutations affecting the interaction of DSPP with collagen I or II could result in the phenotype. Lund et al. [87] suggested a time- and tissue-dependent regulation of the genes coding for collagen I, or epigenetic factors influencing the interaction of collagen I with other extracellular matrix proteins. Further clinical and molecular studies are still required to clarify these observations.

### 3.1.2. DGI and DD with other hereditary defects of collagen

Syndromes associated with collagen mutations and DGI type II and DD are summarized in Table II (see Supplementary Material 1).

### 3.1.3. Ehlers–Danlos syndrome (EDS)

In most instances, patients with EDS have no evidence of dentin dysplasia. A partial duplication of **COL1A2** gene has been demonstrated in a single patient with EDS type VII and opalescent teeth [124]. Moreover EDS type VIIC patients with a nonsense mutation in **ADAMTS2** — enzymes which excise the N-propeptide of procollagens — were recently described with multiple tooth agenesis, dentin structural anomalies, and dysplastic roots [30].

### 3.1.4. Goldblatt syndrome

This rare syndrome (OMIM 184260) combines spondylometaphyseal dysplasia, joint laxity and DGI or dentin dysplasia type II. Deciduous teeth are opalescent whilst the permanent teeth are almost normal [11]. The latter authors found a decrease in synthesis of collagen type I (A1 and A2), and a single-base substitution in the **COL2A1** gene. They proposed that this mutation has sequential effects on tissue-specific regulatory sequences that control the expression of type I collagen genes.

### 3.2. Syndromes associated with DGI without a collagen mutation

Several syndromes are associated with dental findings, which are clinically and radiographically similar to those observed in DGI (Supplementary Material 1, Table III) [65].
3.2.1. Schimke immunoosseous dysplasia (SIOD)

SIOD is an autosomal recessive disorder characterized by spondyloepiphyseal dysplasia, renal dysfunction, and T-cell immunodeficiency. It is due to mutations in \textit{SMARCAL1} (SWI/SNF related, matrix associated, actin dependent regulator of chromatin 1) \cite{10}. da Fonseca \cite{28} reported dental findings resembling DGI. The teeth have a yellowish grey discoloration, bulbous crowns and marked cervical constriction of the primary and permanent molars. The pulp chambers are small or obliterated. Both enamel and dentin are softer than normal (Fig. 4).

4. Syndromes involving dentin anomalies

Besides DGI, abnormal dentin can be seen in disorders involving phosphocalcic metabolism and often growth retardation. Syndromes associated with dentin dysplasia type I are listed in Table IV (Supplementary Material 1).

4.1. Hyperphosphatemic familial tumoral calcinosis (HFTC)

HFTC (OMIM 211900) is a rare autosomal recessive disorder characterized by progressive deposition of calcified masses in cutaneous and subcutaneous tissues, associated with elevated circulating levels of phosphate. The disease was initially found to result from mutations in the \textit{GALNT3} gene mapped to 2q24–q31 (OMIM 601756) \cite{7, 150} and encoding a glycosyltransferase (ppGalNacT3). Mutations in \textit{GALNT3} are also responsible for Hyperostosis–Hyperphosphatemia Syndrome (HHS) \cite{42}. More recently, recessive loss-of-function mutations in \textit{FGF23}, located on 12p13.3, encoding a phosphaturic protein were also identified in HFTC \cite{6, 76}. Interestingly, dominant gain-of-function mutations in \textit{FGF23} gene result in autosomal dominant hypophosphatemic rickets (ADHR, OMIM 605380). Patients with HFTC caused by \textit{GALNT3} mutations have dentin dysplasia with short bulbous roots, pulp stones and partial obliteration of the pulp cavity \cite{144, 59}. In a patient with a \textit{FGF23} mutation, Chefetz et al. \cite{24} observed delayed eruption of permanent teeth and diminished root length. In this group of conditions the dental phenotype may thus orient molecular diagnosis. Physiological interactions between \textit{FGF23} and \textit{GALNT3} await further studies.

4.2. Familial hypophosphatemic vitamin D-resistant rickets

Familial hypophosphatemic vitamin D-resistant rickets or X-linked dominant hypophosphatemia (XLH) presents with growth retardation, rachitic and osteomalacic bone disease, hypophosphatemia, renal defects in phosphate reabsorption and vitamin D metabolism, and dental...
findings [129]. The patients often have multiple periodontal abscesses, but no evidence of dental caries, trauma, or periodontal disease on the corresponding teeth. Radiographic examination of teeth shows root dysplasia and enlarged pulp chamber. The histological examination shows marked globular dentin and increased predentin width [105,13]. The abscesses are thought to be caused by pulp infection, which arise from bacterial invasion through enamel cracks and dentin microcleavage of the teeth [54]. XLH is caused by mutations in the phosphate-regulating endopeptidase gene (PHEX) located in Xp22.2—p22.1.

Various syndromes with dentin anomalies are associated with primordial dwarfism. Primordial “dwarfism” is used to describe patients with severe intrauterine and postnatal growth retardation, and they can be subclassified into three main types: Seckel syndrome, microcephalic osteodysplastic primordial dwarfism (MOPD) type I/III and MOPD type II [98,92]. Variants of MOPD or Seckel-like syndrome have been described [139,16].

4.3. Seckel syndrome

Seckel syndrome (SCKL1, OMIM 210600) is a rare AR disorder characterized by postnatal proportional short stature, microcephaly with mental retardation, and a characteristic “bird-headed” facial appearance. This condition can be caused by mutations in the ATR gene (3q22.1—q24) that encodes the ataxia-telangiectasia and RAD3-related protein [46]. Other loci for Seckel syndromes have been mapped to chromosome 18p11-q11 (SCKL2; OMIM: 606744) [12] and 14q23 (SCKL3; OMIM: 608664) [68]. Dental anomalies have been reported before the molecular subdivision of the syndrome and correlations between dental phenotype and gene mutations have not been reported. Teeth anomalies include atrophic or absent teeth and hypoplasia of the enamel [43]. Kjaer et al. [69] described four siblings with Seckel syndrome. Agenesis of two or more teeth occurred in all four children, and all children lacked the upper lateral incisors. Short roots and taurodontic molars were also observed. Complete and semitaurodontic root shapes were noted in the girls. Contrasting with bone age delay, dental maturation was normal. Seymen et al. [136] reported a seven-year-old boy with microdontia, missing lateral maxillary and central mandibular incisors (permanent dentition) and dentin dysplasia. In two young patients (24 and 34 months) with Seckel syndrome, Buebel et al. [16] reported cleft of the soft palate, hypodontia of maxillary (and in one case mandibular) lateral incisors, and enamel hypoplasia in one patient, but no radiographic examination was performed. Another dental phenotype with proportionate primordial short stature has been reported with hypoplastic alveolar processes, severe microdontia, opalescent teeth, and rootless molars (OMIM 607561) [66,67].

Patients affected with the two types of MOPD can easily be distinguished from those with Seckel syndrome by being disproportionately short and having distinct radiological features [90—92]. The dental phenotype has not been emphasized even though microdontia, hypodontia, and dentin dysplasia occur in this group of patients. Lin et al. [81] described microdontia in both dentitions, bulbous crowns and short roots in patients with MOPD type II. Dentin anomalies vary from dentin dysplasia type I to opalescent rootless teeth [110].

Other rare syndromes with an abnormal dentin phenotype report are listed in Table V (Supplementary Material 1).

5. Syndromes with supernumerary teeth (hyperdontia)

Usually hyperdontia is an isolated feature, but when many supernumerary teeth are observed they could be part of a syndrome.
5.1. Cleidocranial dysplasia

Cleidocranial dysplasia is an AD disorder affecting bone and teeth development and is caused by mutations in \textit{RUNX2}, a gene encoding an osteoblast-specific transcription factor which maps to 6p21 (OMIM 119600) [104]. The symptoms include hypoplastic calvarial bones and clavicles. Dental abnormalities include supernumerary teeth (sometimes leading to a “third dentition”), delayed eruption, failure of exfoliation of the primary dentition, and malocclusion (Fig. 5).

5.2. Familial adenomatous polyposis (FAP), Gardner syndrome

Gardner syndrome, a clinical variant of FAP, is an autosomal dominant disease characterized by gastrointestinal polyps, multiple osteomas, and skin and soft tissue tumours (OMIM 175100, \textit{APC Adenomatous Polyposis of the Colon, 5q21–q22}) [53]. Cutaneous findings include epidermoid cysts, desmoid, and other benign tumours. Polyps have a 100% risk of undergoing malignant transformation; consequently, early identification of the disease is critical.

Fader et al. [40] first reported impacted teeth, supernumerary teeth, congenitally missing teeth, and abnormally long and pointed roots of the posterior teeth in Gardner syndrome [21]. Järvinen et al. [63] found dental anomalies in only 18% of patients but jaw osteomas were very frequent. Occult radio-opaque osteomas of the jaw are an important early sign of the condition, preceding clinical and radiological evidence of colonic polyposis. The mandible is the most common location; however, osteomas may occur in the skull and the long bones. Thakker et al. [148] presented a diagnostic scoring system, the Dental Panoramic Radiographs Score (DPRS). This takes into account the nature, extent, and sight of osseous and dental...
changes, as well as the incidence of the anomaly in the general population. The DPRS is a reproducible and valid index for assessing individuals at 50% risk of FAP [1].

The APC gene product indirectly regulates transcription of a number of critical cell proliferation genes, loss of APC function increases transcription of β catenin targets. These targets include cyclin D, C-myc, ephrins and caspases. APC also interacts with numerous actin and microtubule associated proteins. APC itself stabilizes microtubules (http://atlasgeneticsoncology.org/Genes/APC118.html). The relationship between APC mutations and dental abnormalities remains controversial [29,114].

5.3. Nance–Horan syndrome

Nance–Horan syndrome is an X-linked disorder characterized by congenital cataracts, dysmorphic features, anomalous form of teeth and in some cases mental retardation (OMIM 302350). The syndrome is caused by mutations in the NHS gene, whose function is not known. Screwdriver shaped and supernumerary incisors are reported [151].

6. Syndromes with congenital absence of teeth

Missing teeth, either hypodontia, oligodontia, or anodontia are a very common and relatively non-specific finding in MCA syndromes (see part 1). It is a key feature of the ectodermal dysplasias group (Supplementary Material 1, Table VI), where it is associated with abnormal shape of the remaining teeth, whereas the present teeth are often normal in the other syndromes (Supplementary Material 1, Tables VII, VIII, IX). We review some of these disorders below. Other entities are summarized in Table X (Supplementary Material 1).

6.1. Down syndrome

Congenital absence of teeth has been reported in 69.8% of females and 90.7% of the males with Down syndrome, in a Danish population [128]. Lateral maxillary incisors, lower central incisors and second premolars are the most commonly missing teeth. One or both primary upper lateral incisors were missing in more than 10% of the patients, and peg-shaped maxillary lateral incisors are seen in 10% [47]. Shapira et al. [137] studied dental anomalies in 34 individuals with Down syndrome in Israel. Excluding third molars, 59% had missing teeth and 25% of the individuals had small or peg-shaped upper lateral incisors.

6.2. Wolf–Hirschhorn syndrome

The Wolf–Hirschhorn syndrome (WHS) is caused by deletions of a subterminal region (WHCR) of chromosome 4p. Reported dental abnormalities are delayed eruption, fusion of incisors and oligodontia. A single case with congenital tooth agenesis has been described [17]. Oligodontia is probably due to the loss of one copy of MSX1, which is located at 4p16.1 [108].

6.3. Holoprosencephaly

Holoprosencephaly (HPE) is a developmental field defect in which midline cleavage of the forebrain and craniofacial structures is impaired. HPE is etiologically heterogeneous, caused by teratogens or genetic factors. It occurs in 1/16,000 newborns, half of whom have chromosomal
anomalies [126]. Based on the analysis of HPE patients with chromosome rearrangements, at least 16 loci for the disorder, have been assigned; seven genes are identified (Supplementary Material 1, Table VII). Mutations and deletions in these genes are observed in roughly 20% of non-chromosomal cases. The sonic hedgehog gene (SHH) at 7q36 (HPE3 locus) is the most frequently involved. An extreme intrafamilial phenotypic variability is observed, ranging from the classical phenotype with alobar HPE and typical severe craniofacial abnormalities to very mild clinical signs of choanal stenosis or solitary median maxillary central incisor (SMMCI) (Fig. 6).

6.4. Kallmann syndrome

Kallmann syndrome is a developmental disease that combines hypogonadotropic hypogonadism and anosmia/hyposmia. The prevalence is estimated at 1/10,000 in males and at
Kallmann syndrome is genetically heterogeneous. An X-linked form is due to mutations in the \textit{KAL1} gene (Xp22.3) \cite{51}. An autosomal dominant form is due to mutations in fibroblast growth factor receptor 1 (\textit{FGFR1}) (KAL2 locus at 8p12) \cite{33}. A rare autosomal recessive form is reported for which no causal mutation has been identified. \textit{KAL1} and \textit{KAL2} mutations account for only 20\% of Kallmann syndrome \cite{33,130,131,2,120}.

To date, dental agenesis is described only in \textit{KAL2}, and may or may not be associated with cleft palate or lip. The type of dental anomalies varies from a single central maxillary incisor to lateral maxillary incisor agenesis, and premolar agenesis. In some cases the first four permanent molars and mandibular canine are missing \cite{131} (Supplementary Material 1, Table VIII).

6.5. Ectodermal dysplasias

Ectodermal dysplasias form a large and complex group of disorders characterized by various combinations of defects in hair, nails, teeth and sweat glands, either isolated or associated with malformations. Of the approximately 170 clinical types of ectodermal dysplasias described so far, a gene is identified in less than 30. The clinical classification is more complex than the genetic one, and some genes have been associated with many clinical entities. Lamartine \cite{75} proposed a new classification of ectodermal dysplasias based on the function of the protein encoded by the mutated gene. He divided ectodermal dysplasias into four groups: cell–cell communication and signalling; adhesion; regulation of transcription; and development (Supplementary Material 1, Table VI).

6.5.1. Hypohidrotic ectodermal dysplasia (HED)

The X-linked form of the disease (XLHED, OMIM 305100) is caused by \textit{EDA} (ectodysplasin A) gene mutations and represents 75–95\% of familial and 50\% of sporadic cases \cite{102,133,115,152}. By alternative splicing \textit{EDA} encodes various isoforms of a signalling molecule of the TNF-related ligands family. The \textit{EDA} signalling pathway involves at least two isoforms of 391 and 389 amino acids: ectodysplasin \textit{EDA-A1} and \textit{EDA-A2}. The autosomal dominant and recessive forms of HED have been associated with mutations in the \textit{EDAR} (\textit{EDA Receptor}) gene \cite{102} or the \textit{EDARADD} (\textit{EDAR-associated death domain}) gene \cite{52}. Mutations in \textit{EDAR} account for one-quarter of non-\textit{EDA}-related HED \cite{23}. Headon et al. \cite{52} found that \textit{EDAR} is activated by \textit{EDA} and uses \textit{EDARADD} as an adaptor to build an intracellular signal-transducing complex.

Common clinical findings are fine, dry, brittle and sparse hair. The skin is thin, glossy, smooth and dry with hypohidrosis. In the X-linked form of HED, females have sparse, thin scalp hair and mosaic patchy distribution of skin anomalies. Many of them have abnormal teeth. Patients with full-blown HED have sparse hair, diminished sweating and decreased salivary and lacrimal secretions \cite{106}. Oligodontia is almost constant and the remaining teeth are misshapen (Figs. 7 and 8). Complete anodontia is occasionally seen. When present, upper incisors, upper and lower first molars, and lower second molars are significantly smaller and misshapen. Seventy-three percent of obligate heterozygous females of the X-linked form have one or more missing teeth, and most have smaller teeth. These findings suggest that the X-linked form of HED is a highly penetrant X-linked trait with intermediate expression in the heterozygous female. Carrier detection of the X-linked form is often possible by dental examination: small, peg-shaped incisors and canines, and missing teeth are usually found, and the
Fig. 7. Ectodermal dysplasia with abnormal-shaped, conical incisor and missing teeth.

Fig. 8. Ectodermal dysplasia. (A) Face and (B) labial view.
deciduous second molar teeth usually show taurodontism [106,143,45]. Studies in two families showed that X-linked non-syndromic hypodontia resulted from EDA mutations [146,147].

6.5.2. Incontinentia pigmenti, hypohidrotic ectodermal dysplasia and immune deficiency (HED-ID)

Incontinentia Pigmenti (IP) is an X-linked dominant condition, lethal in males. IP affects skin, teeth, eyes and the nervous system. The most common mutation is a genetic rearrangement, resulting in deletion of part of the NEMO (NFkB essential modulator) gene [149]. The disease shares some characteristics with X-linked ectodermal dysplasia [8]. Dental anomalies are present in 70% of the patients [101,157,3]. Both dentitions are affected: hypodontia, pegged or conical teeth and delayed eruption are reported in 30% of cases (Fig. 9).

A form of ectodermal dysplasia with immunodeficiency segregates as an X-linked recessive trait [164,34]. Hypohidrosis and abnormal dentition are similar to those in other forms of

Fig. 9. Incontinentia pigmenti. (A) Face and (B) orthopantomogram.
ectodermal dysplasias. Affected males manifest with dysgammaglobulinemia and infections can be lethal. Female carriers show no clinical signs of immunodeficiency but may have hypodontia and conical teeth. Mutations in NEMO have been found in HED-ID patients. IKK-gamma is required for activation of NFkB, a transcription factor transducing TNF signalling. NFkB transduces signalling via ectodysplasin/EDAR, which presumably explains the phenotypic similarities between HED and HED-ID [73,71]. Dental examination of four families with HED-ID studied by Zonana et al. [164] showed hypodontia/oligodontia in the primary and permanent dentition, as well as cone-shaped teeth. Ku et al. [72] suggested screening NEMO in boys with conical incisors and unusual infectious diseases.

The osteopetrosis—lymphedema—anhidrotic ectodermal dysplasia-immunodeficiency (OL-EDA-ID) syndrome and IP are allelic. Loss of function of NEMO is responsible for IP and hypomorphic mutations for OL-EDA-ID. The dental phenotype is poorly described in the literature but delayed eruption and incomplete dentition are mentioned [95,37].

6.5.3. p63 mutation related syndromes

Several autosomal dominant syndromes are caused by mutations in the p63 gene on 3q27. p63 is involved in growth and differentiation of ectoderm-derived oral tissues. The p63 syndrome family includes the ectodermal dysplasia—ectrodactyly—cleft lip and palate syndrome type 3 (EEC3), ankyloblepharon—ectodermal dysplasia—clefting syndrome (AEC), acro-dermato-ungual-lacrimal-tooth syndrome (ADULT), limb—mammary syndrome, and non-syndromic split-hand/foot malformation (Supplementary Material 1, Table VI-b). All types are AD with variable expression. A clear genotype—phenotype correlation can be recognized for EEC and AEC syndromes [15]. EEC syndrome is genetically heterogeneous: besides the common EEC (EEC3), EEC type 1 syndrome maps to 7q11.2—q21.3 [123] and EEC type 2 to the pericentromeric region of chromosome 19 in a Dutch kindred [112].

The ectodermal dysplasia features seen in the patients with EEC syndrome are sparse hair, dystrophic nails, hypopigmentation or pigmented nevi of the skin, and abnormal dentition [18,125]. Anomalies of the lacrimal ducts, urogenital defects, and conductive hearing loss have been reported [125]. Congenitally missing permanent teeth and conical teeth are common. Buss et al. [18] reported dental features in 24 patients with EEC syndrome: the permanent dentition of all patients is affected by oligodontia and microdontia. The teeth are not as strikingly conical as in X-linked EDA, being more often straight-edged with gaps; taurodontism is also reported. The number of teeth is normal in the primary dentition, but with abnormal morphology of the tooth crowns. Chranowska et al. [26] described a family with anodontia of permanent teeth as the sole clinical sign of EEC. There are no available data on possible differences in dental anomalies between EEC type 3 and the much rarer types 1 and 2. Hypodontia has been reported in the AEC syndrome with p63 mutations [97]. However, neither dental anomalies nor p63 mutations have been reported in the split-hand/foot malformation (SHFM, OMIM 183600) [58].

6.6. Lacrimo-auriculo-dento-digital syndrome

Lacrimo-auriculo-dento-digital syndrome (LADD, OMIM 149730) is an autosomal dominant MCA disorder characterized by aplasia, atresia or hypoplasia of the lacrimal and salivary systems, cup-shaped ears, hearing loss, dental and digital anomalies. The dental features include small and peg-shaped or absent lateral maxillary incisors and mild enamel dysplasia [56,20]. LADD is genetically heterogeneous. Rohmann et al. [127] identified heterozygous missense
mutations in FGFR2, FGFR3 and FGF10. Additional LADD loci are on chromosomes 10q26, 4p16.3 and 5p13–p12.

Mutations in FGFR2 cause several craniosynostosis syndromes (Pfeiffer, Crouzon, and Apert syndromes). Mutations in FGFR2 causing LADD are situated in the tyrosine kinase domain, which appears to be the critical domain for lacrimal, and salivary gland development, as well as morphogenesis of ears, teeth, and digits. Loss-of-function mutations in FGF10 are described in aplasia of the lacrimal and salivary glands (ALSG, OMIM 180920) [38]. Recently Milunsky et al. [100] found a nonsense mutation (K137X) of FGF10 in a 19-year-old mother with ALSG and in her 2-year-old daughter with LADD syndrome.

6.7. Axenfeld–Rieger malformation and Rieger syndrome

The Axenfeld–Rieger malformation (ARM) consists of various anomalies of the anterior chamber of the eye [141,25]. Its incidence has been estimated as 1/200,000 [47]. Fifty percent of affected individuals have a propensity to develop glaucoma. Rieger syndrome is characterized by the association of Rieger–Axenfeld malformation with dental, craniofacial, and somatic anomalies, such as redundancy of periumbilical skin [70]. Dental abnormalities are the key features to differentiate Rieger syndrome from the Axenfeld–Rieger malformation [32].

The predominant anomaly is congenitally missing teeth in both the deciduous and permanent dentitions. Incisors and canines are most often absent. The second premolars and molars are occasionally missing. Other tooth abnormalities include enamel hypoplasia, conical-shaped teeth, short roots, taurodontism, and delayed eruption [25,14,60] (Fig. 10). Patients with PITX2 mutations have been reported with normal number of teeth and short roots [64].

At least seven loci are associated with ARM, and three genes are identified: PITX2, FOXC1 and GJA1 (Supplementary Material 1, Table IX). Dominant negative and dominant positive

Fig. 10. Axenfeld–Rieger syndrome. (A) Oral view of abnormal-shaped maxillary incisor and agenesis of lateral incisors in upper and lower arches and (B) orthopantomogram.
mutations of the homeodomain transcription factor \textit{PITX2} contribute to the variable ARM phenotype [39]. Berry et al. [9] identified a functional link between the transcription factors, \textit{FOXC1} and \textit{PITX2}, which underpins the similar ARM phenotype caused by mutations of these genes. Furthermore, \textit{PITX2A} can function as a negative regulator of \textit{FOXC1} transactivity. Cella et al. [22] observed a family with concomitant structural alterations in the \textit{FOXC1} and \textit{GJA1} genes resulting in a less severe phenotype than that observed in patients with the \textit{FOXC1} mutation alone within the same family.

6.8. Johansson—Blizzard syndrome

The Johansson—Blizzard syndrome (JBS, OMIM 243800) is an AR disorder characterized by congenital insufficiency of the exocrine pancreas with malabsorption, hypoplasia of the alae nasi, congenital deafness, hypothyroidism, postnatal growth retardation, mental retardation, midline scalp defects, and absent permanent teeth. Zenker et al. [161] mapped the gene to 15q14–q21.1 and described two mutations in the \textit{UBR1} gene. The dental phenotype includes delay of primary teeth eruption, microodontia, and severe oligodontia of the permanent teeth. The first mandibular permanent molars are the most conserved teeth followed by maxillary first molars and central incisors. Additional or missing tubercles are noted on dental crowns [162].

6.9. Wilkie oculo-facio-cardio-dental syndrome

Wilkie [154] reported a syndrome characterized by heart defects (ASD and VSD), microphthalmia, cataracts, and hyperplastic primary vitreous. The nose is narrow with an enlarged tip and notching of the alae nasi. Cleft palate, genital, digestive and digital anomalies may be present and laterality defects (asplenia and dextrocardia) have been reported [55,134]. There are missing teeth and delayed eruption of secondary teeth. The crowns and roots of several incisors and canines are unusually large with radiculomegaly, and peg-shaped incisors [96,113] (Fig. 11). Wilkie syndrome is X-linked dominant, with lethality in males and skewed X-inactivation and results from mutations in the \textit{BCOR} gene located in Xp11 [107]. The protein is an interacting corepressor of \textit{BCL6}, which is required for germinal centre formation and may influence apoptosis.

Other syndromes with tooth agenesis are listed in Table X (Supplementary Material 1).

![Fig. 11. Oculo-facio-cardio-dental syndrome: oral view with macrodontia of maxillary central incisors.](image)
7. Conclusion

Dental anomalies are innumerable in MCA syndromes. Although their true clinical importance may be secondary in many complex and disabling disorders, good characterization of the dental phenotype may be helpful in early recognition of some progressive or highly variable conditions. The dental phenotype could be similar for different genotypes, adverse environment or systemic anomalies, and thus the search of etiologic factors must be very accurate. They could sometimes be pivotal in the strategy of molecular screening. Clinical anomalies in syndromes are also a mean to make sense of the developmental pathways required for proper tooth development.

Dental dysmorphology is still largely an unknown field. In many cases, dental dysmorphism is poorly or even incorrectly reported, partially because clinical dysmorphologists are poorly trained in recognizing and accurately describing dental defects (including their radiological aspects) and partially because dentists are often unaware of the extra-odontologic aspects of the oral anomalies, with which they are associated. This review illustrates the importance to note all other organ findings in case of dental abnormalities. It illustrates the importance of teamwork between odontologists and geneticists.

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Appendix. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejmg.2008.05.003.

References


