Review

The genetic basis of inherited anomalies of the teeth: Part 1: Clinical and molecular aspects of non-syndromic dental disorders

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Abstract

The genetic control of dental development represents a complex series of events, which can very schematically be divided in two pathways: specification of type, size and position of each dental organ, and specific processes for the formation of enamel and dentin. Several genes linked with early tooth positioning and development, belong to signalling pathways and have morphogenesis regulatory functions in morphogenesis of other organs where they are associated with the signalling pathways. Their mutations often show pleïotropic effects beyond dental morphogenesis resulting in syndromic developmental disorders. Some genes affecting early tooth development (*MSX1*, *AXIN2*) are associated with tooth agenesis and systemic features (cleft palate, colorectal cancer). By contrast, genes involved in enamel (*AMELX*, *ENAM*, *MMP20*, and *KLK4*) and dentin (*DSPP*) structures are highly specific for tooth. Mutations in these genes have been identified as causes of amelogenesis imperfecta, dentinogenesis imperfecta, dentin dysplasias and anomalies of teeth number (hypo-, oligo and anodontia), which only partially overlap with the classical phenotypic classifications of dental disorders. This review of genetic basis of inherited

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anomalies describes, in this first paper, the molecular bases and clinical features of inherited non-syndromic teeth disorders. And in a second part, the review focus on genetic syndromes with dental involvement.

1. Introduction

Advances in molecular genetics and the Human Genome Project have provided substantial progresses regarding the identification of genes involved in the pathogenesis of human diseases. These include dental diseases affecting enamel and dentin formation and anomalies in teeth number. Genetic diseases affecting tooth structure have been classified by the affected tissue (enamel versus dentin), by their specificity (syndromic versus non-syndromic) and their pattern of inheritance: autosomal dominant (AD), autosomal recessive (AR), or X-linked recessive (XLR).

In this paper, we will review the clinical and molecular aspects of non-syndromic inherited dental disorders. A twin paper will focus on genetic syndromes with dental involvement.

In human embryo, deciduous and permanent teeth develop from the oral ectoderm and the underlying neural mesenchymal cells, which have migrated from the cranial neural crest to the facial process. During the 6th week of human development, a line of oral epithelium cells thickens to form the dental lamina, which develops several buds, invading the underlying mesenchyme. The epithelial compartment of each bud evaginates to form a cupule-shaped structure, the enamel organ, with an inner part, the enamel reticulum, and an epithelial coverage. The enamel organ covers a densified mesenchymal tissue, the dental papilla. Mesenchymal cells of the dental papilla, that are adjacent to the enamel organ, differentiate into odontoblasts and start to secrete dentin, the inner tissue of teeth. The central part of the papilla forms the dental pulp. Epithelial cells adjacent to differentiating odontoblasts differentiate into ameloblasts, that secrete enamel, the outer cover of teeth. Mineralization begins at the tips of the cusps and proceeds towards the cervical area. Root development follows the crown formation. Reciprocal interactions of the epithelial and mesenchymal tissues regulate dental development [1]. The mesenchyme surrounding the enamel organ and the growing roots form a fibrous structure, the periodontal ligament that ties the tooth to the alveolar bone [2]. While this process leads to the differentiation of deciduous teeth, the pedicle that connects the growing enamel organ to the surface epithelium produce an expansion that follows the same differentiation process, and lead to the formation of permanent teeth. A distal extension of the dental lamina provides the tooth germs for permanent molars. Simultaneously, the outer part of the dental lamina degenerates, separating the tooth from the gingival epithelium. Biomineralization begins during 14–18 weeks of pregnancy, and the crowns of all 20 primary teeth are partly mineralized at birth. All permanent tooth crowns except the third molars have begun their mineralization at the age of 6 years.

Studies of odontogenesis, mostly using mouse teeth as models, have indicated that the position, number, size and shape of different teeth are under genetic control [3]. Tooth development is initiated by signals from the epithelial dental lamina to the mesenchyme [4]. Thereafter, the mesenchyme regulates epithelial morphogenesis. Regulation of development is mediated by complex interactions between the epithelium and mesenchyme. The centre of the epithelial bulk: the enamel knot is functioning as an important signalling centre regulating tooth shape [5]. During tooth development, the epithelium and mesenchyme interact through

different families of signalling molecules and their receptors. These comprise the transforming growth factor β (TGFβ), bone morphogenetic proteins (BMP), fibroblast growth factors (FGF), epidermal growth factor (EGF), and the hedgehog (Hh) and wingless (Wnt) families [6]. In addition to these signals, the model proposed by Thesleff [7] also includes several genes, which are regulated by the signals in the responding tissues (Fig. 1). Mutations in many of these genes already have been shown to cause dental defects in mice as well as in humans [8].

2. Hereditary enamel defects

Enamel is a unique tissue characterized by a low protein and high mineral content. Ameloblasts play two roles during amelogenesis. They secrete the four major enamel matrix proteins and proteases: amelogenin (80–90%), ameloblastin (5–10%), enamelin (3–5%), and enamelysin (1%) [9]. And later, they contribute to the maturation of the enamel, which is accompanied by a loss of organic matrix and an increase in mineralization. Enamel is made up of strictly organized, oriented and tightly packed crystallites. These crystallites are extremely long relative to their thickness. They generally extend from the underlying dentin toward the surface of the tooth and are organized into bundles, called prisms. Because of its peculiar properties, enamel mirrors and records, during its development, the variations in metabolic status of the individual. Hence enamel anomalies may reflect both environmental and systemic disturbances. Diagnosis of an enamel defect requires a detailed record of the clinical history of the patient, the potential exposure to environmental factors and the family history (Fig. 2). Defects in genes encoding enamel proteins generally cause enamel malformations without affecting other parts of the body, although several genetic syndromes are associated with enamel defects.

Amelogenesis imperfecta (AI) is a genetically and clinically heterogeneous group of inheritable disorders primarily affecting formation of enamel. The phenotype varies from localized
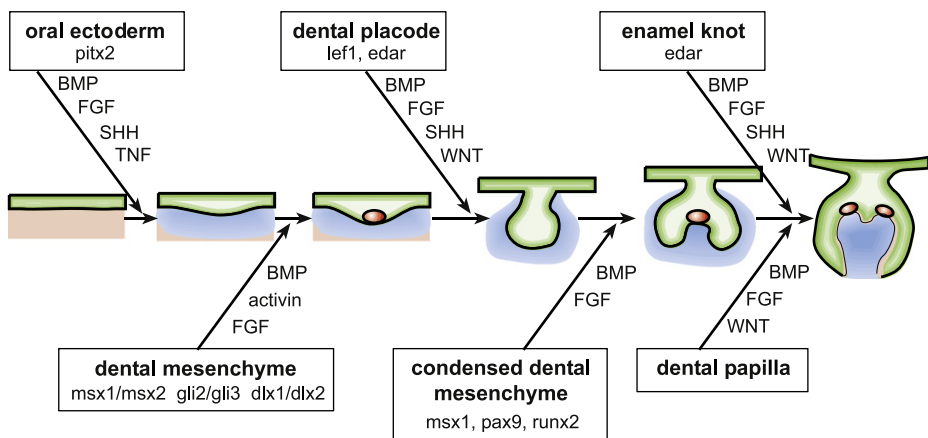

Fig. 1. Model of the molecular regulation of tooth development from initiation to crown morphogenesis. Courtesy of I Thesleff. Interactions between epithelial (green) and mesenchymal tissues (blue) are mediated by signal molecules (BMP = bone morphogenetic proteins; FGF = fibroblast growth factors; SHH = sonic hedgehog; TNF = tumor necrosis factor; WNT = wingless-type). These signals operate throughout development and regulate the expression of genes in the responding tissues (shown in boxes). Signalling centres (red) appear in the epithelium reiteratively and secrete locally more than 10 different signals that regulate morphogenesis and tooth shape. The genes mentioned have been shown to be necessary for normal tooth development.
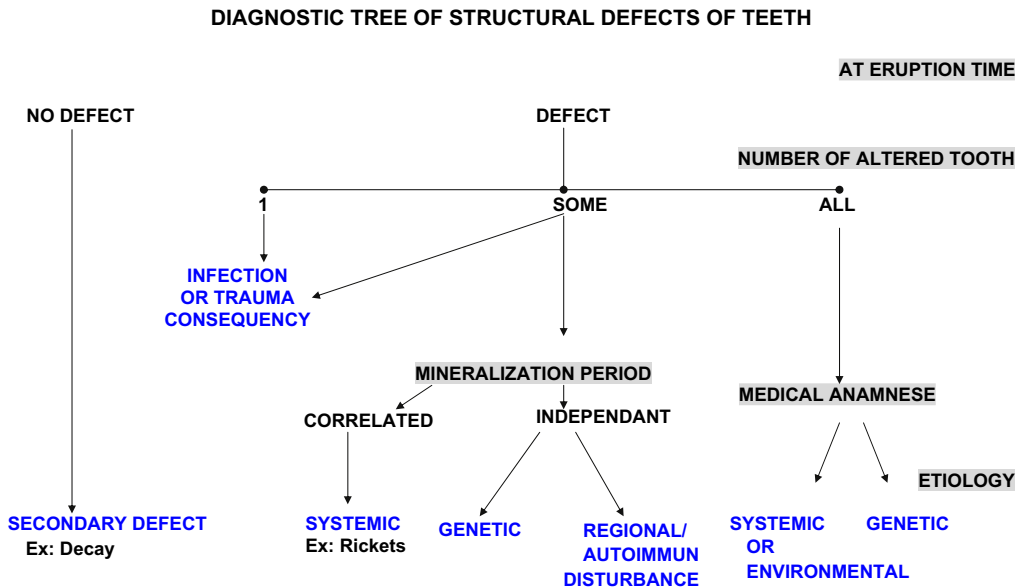
DIAGNOSTIC TREE OF STRUCTURAL DEFECTS OF TEETH

AT ERUPTION TIME

NO DEFECT		DEFECT	

NUMBER OF ALTERED TOOTH

1   SOME   ALL

INFECTION
OR TRAUMA
CONSEQUENCY

MINERALIZATION PERIOD

CORRELATED   INDEPENDANT

MEDICAL ANAMNESE

ETIOLOGY

SECONDARY DEFECT   SYSTEMIC   GENETIC   REGIONAL/   SYSTEMIC   GENETIC
Ex: Decay   Ex: Rickets   AUTOIMMUN   OR
                                                      DISTURBANCE   ENVIRONMENTAL

Fig. 2. Diagnostic tree of stuctural defects of teeth.

enamel deficiencies (hypoplasia) to complete absence of it (aplasia). The prevalence of AI varies in different populations, ranging from 1 in 700 in to 1 in 4000 [10,11]. The AI can be autosomal dominant, autosomal recessive, or X-linked. One large epidemiological study of 51 Swedish AI families segregating for AI showed approximately 6% of cases to be X-linked, 63% autosomal dominant (AD), and 12% autosomal recessive (AR) [12]. The remaining 19% of AI cases were sporadic with neither family history nor discernable mode of transmission. The distribution of AI types is also known to vary in different populations. Autosomal recessive AI was the most prevalent AI type in a study evaluating 70,000 Israeli school children [13]. Enamel findings in AI are highly variable, ranging from deficient enamel formation (hypoplastic AI) (Figs. 3A,B and 4) to defects in the mineral and protein content (hypomineralized and hypomature AI). In the latter forms, the enamel discloses more or less severe discoloration, from opaque white enamel to yellowish or brown appearance (Table 1, Figs. 5 and 6). The dentin itself can be more or less exposed, after the loss of the enamel cap.

Classifications of AI are primarily based on phenotype and mode of inheritance. The most commonly used classification was proposed in 1988 by Witkop [14], and revised by Nusier in 2004 [15] (Table 2). Although this system allows some apparent ordering of AI, practical application of Witkop system is hampered by the important intrafamilal variability of the AI phenotype and the lack of close correlation between the AI type, and the molecular defect [16−18]. Based on enamel appearance and hypothesized developmental defects, AI can be classified into hypoplastic (secretory defect), hypocalcified (mineralization defect), and hypomaturation (protein processing and crystallite maturation defect) forms [19]. A diagnostic tree for non-syndromic AI is presented in Fig. 7.

Although AI is considered here as a non-syndromic defect, many other dental anomalies may be associated with the enamel defect: pulp calcification, taurodontism, delayed eruption and sometimes, gingival overgrowth [20]. The formation of maxillary and mandibular bones
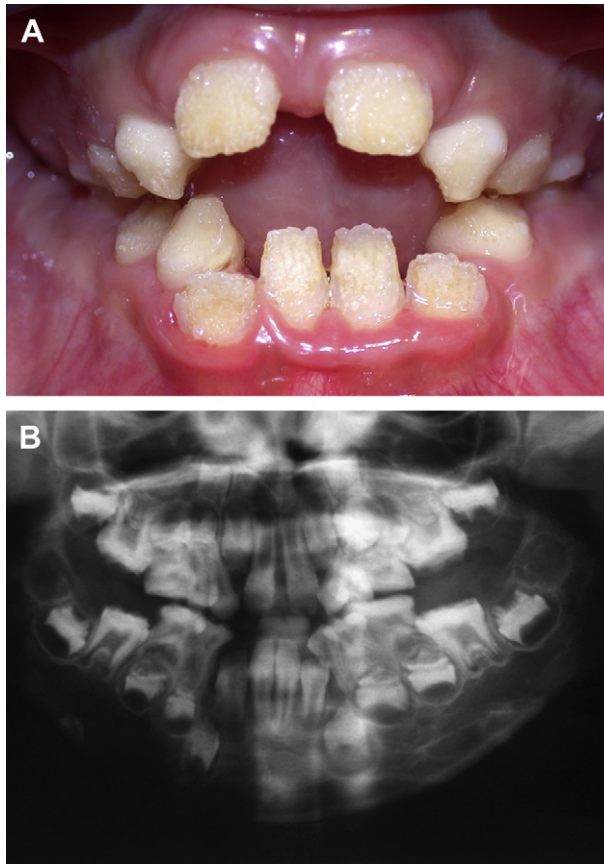
Fig. 3. Amelogenesis imperfecta hypoplastic generalized: A. oral view, B. orthopantomogram.

may be abnormal, leading frequently to open-bite malocclusion (Fig. 3A), less commonly to prognathism [21]. The pathogeny of these oral anomalies is poorly understood and controversial (local mechanisms, environmental factors or genetically determined anomaly of craniofacial development) [22].

Fig. 4. Amelogenesis imperfecta hypoplastic localised: pitted type, oral view.

Table 1

Clinical and radiographic characteristics of Amelogenesis Imperfecta applied to the classification of Witkop revised [14,15] (in italic)

	AI type	Clinical aspect	Radiographic aspect
Hypoplastic (*type I*)	Hypoplastic, generalized (*type IG*) (Fig. 3A)	Thin, patchy, rough aspect of the enamel layer	Hypoplasia of the enamel layer, more pronounced on the coronal two-thirds
		Reduced contact between the teeth	Reduced thickness of enamel
	Hypoplastic localised (*type I A–F*) (Fig. 4)	Similar aspect, but limited part of the crown	Hypoplasia may be difficult to observe
Hypomineralized	Hypocalcified (*type III*) (Fig. 5A)	After eruption, the enamel persists only on the cervical part	Normal thickness of the enamel before tooth eruption
			Enamel radiolucency similar to the dentin
	Hypomature (*type II*) (Fig. 6)	Chalky appearance, with orange, brown or white colour	Normal thickness of the enamel
			Enamel radiolucency slightly higher than dentin

2.1. Hereditary amelogenesis imperfecta with autosomal dominant inheritance

Most AI are dominantly inherited, with major intrafamilal variability in expressivity [23]. The most commonly affected gene is enamelin (*ENAM* (4q21) [24] AIH2-OMIM 104500). *ENAM* mutations are preferentially associated with hypoplastic AI [25]. Eight enamelin mutations have been identified at day (two of these are however associated with a recessive transmission inheritance) (see Supplementary Material Table I). In a family with AI type hypoplastic-hypomaturation with taurodontism and autosomal inheritance (AIHHT), a mutation was reported within the homeodomain of *DLX3* (17q21) [26]. Previous studies have shown a *DLX3* mutation outside the homeodomain associated with tricho-dento-osseous syndrome (TDO), suggesting that TDO and some forms of AIHHT are allelic [27].

Several other candidate genes proposed on the basis of their expression in ameloblasts were considered: tuftelin (*TUFT1*) (1q21) [28], ameloblastin (*AMBN*) (4q21) [29], amelotin (*AMTN*) (4q13.3) [30]. Moreover AI has been mapped to 8q24.3 in a large pedigree, segregating an

Fig. 5. Amelogenesis imperfecta hypomineralized hypocalcified type: oral view in mixed dentition.
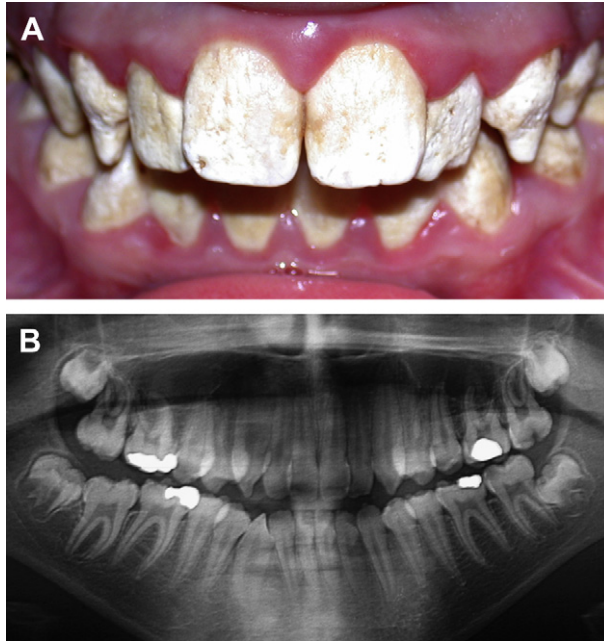
Fig. 6. Amelogenesis imperfecta hypomineralized- hypomatured, A: oral view, B: orthopantomogram.

autosomal dominant form [31]. In several surveys, all known loci have been excluded [23,32,33].

2.2. Amelogenesis imperfecta with autosomal recessive (AR) inheritance (ARAI)

In a large study of 20 consanguineous families, probands presented with a generalized hypoplastic AI phenotype and an open-bite malocclusion. All heterozygous carriers had localised hypoplastic enamel pitting defects, but none had open-bite. In most families, ARAI is also linked to mutations of the enamelin gene [34]. The authors suggest that the phenotype associated with one *ENAM* mutation is dose dependent such that ARAI with open-bite malocclusion segregates as a recessive trait, and enamel pitting as a dominant trait (OMIM 204650) [34]. The major protease genes of enamel development: the kallikrein 4 gene (*KLK4*) (19q13.4) [35], and the enamelysin gene (matrix metalloproteinase 20: *MMP20*, OMIM 604629) (11q22.3–q23) [36,37] are associated with recessive forms of the pigmented hypomature type of AI (see Supplementary Material Table I).

2.3. Amelogenesis Imperfecta related to X chromosome (AIH1, AIH3)

X-linked AI, accounts only for 5% of AI cases [10]. Amelogenin gene is located at Xp22.1–p22.3 (AIH1 locus, *AMELX*, OMIM 301200) and Yp11.2 (*AMELY*). *AMELY* locus encodes a functional protein, although its level of expression is only 10% of that of the *AMELX* locus on the X chromosome [38]. A third locus AIH3 has been mapped in Xq22–q28 (OMIM 301201) [39]. Fifteen mutations have been reported in *AMELX* (see Supplementary Material Table II). No pathogenic mutation of *AMELY* has been reported in so far, and

Table 2

Classification of amelogenesis imperfecta proposed by Witkop (1988) [14], revised by Nusier et al. 2004 (italic) [15]

Type I Hypoplastic
   IA — hypoplastic, pitted AD
   lB — hypoplastic, local AD
   IC — hypoplastic, local AR
   IC — local hypoplastic AR
   ID — hypoplastic, smooth AD
   IE — hypoplastic, smooth X-linked dominant
   IF — hypoplastic, rough AD
   IG — enamel agenesis, AR
   IG — generalized thin hypoplastic AR
Type II Hypomaturation
   IIA — hypomaturation, pigmented AR
   IIA — pigmented hypomaturation AR
   IIB — hypomaturation, X-linked recessive
   IIC — hypomaturation, snow-capped teeth, X-linked
   IID — hypomaturation, snow-capped teeth, AD?
Type III Hypocalcified
   IIIA — AD
   IIIB — AR
   IIIB — hypocalcified AR
Type IV Hypomaturation-hypoplastic with taurodontism
   IVA — hypomaturation-hypoplastic with taurodontism, AD
   IVB — hypoplastic-hypomaturation with taurodontism, AD

Y-linked inheritance of AI has never been reported. No gene has been associated with the AIH3 locus.

The colour of the teeth varies from yellow to brown, with or without opacities. The teeth are of variable size, from normal to microdontia, depending on enamel thickness. Surface can be smooth or rough. Carrier females disclose a specific striated pattern of AI [40]. This vertical
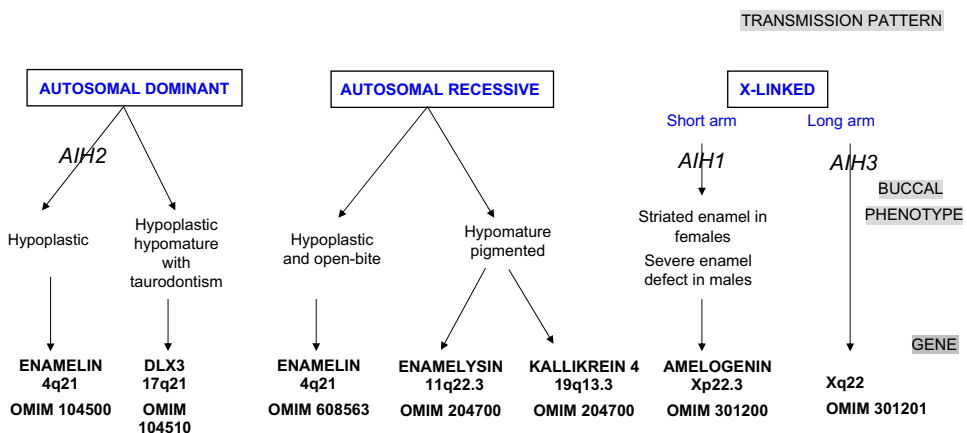

Fig. 7. Diagnostic tree of non-syndromic amelogenesis imperfecta. Major clinical variations could be observed considering the important variability of the AI phenotype, even in a single patient or in a same family. Candidate genes: ameloblastin (4q21), tuftelin (1q21), amelotin (4q13.3) or gene related with syndromic diseases (*MSX2*) are not included in this clinical diagnostic tree.

grooving reflects columns of normal and abnormal ameloblasts activity laid down by (randomly activated) clones of normal or defective ameloblasts, and is an historical example of lyonization [41].

3. Hereditary dentin defects

Bone and dentin extracellular matrix proteins are similar, consisting primarily of type I collagen, acidic proteins and proteoglycans. Collagen forms the lattice for deposition of calcium and phosphate for formation of carbonate apatite. The non-collagenous proteins (NPC) are believed to control initiation and growth of the crystals. The NPCs of the dentin, even though present in small quantities relative to collagen, are of significant functional importance in the mineralization process. Dentin matrix protein 1 (DMP1), dentin sialoprotein (DSP) and dentin phosphoprotein (DPP) play a regulatory role in dentinogenesis [42].

Shields (1973, 1983) have classified dentin defects associated with genetic disorders as dentinogenesis imperfecta (DGI) type I, type II, and type III and dentin dysplasia (DD) type I and type II [43,44]. DGI type I is the dental manifestation in individuals with osteogenesis imperfecta (OI), an autosomal dominant disorder that affects bone. DGI-II, DGI-III, and DD-II with various dental phenotypes appear to occur as an isolated trait, which is usually inherited by an autosomal-dominant hereditary transmission. DGI-II, DGI-III, and DD-II have been mapped by linkage analysis to chromosome 4q21 [45–47]. Mutations in dentin sialophosphoprotein (*DSPP*) gene have been demonstrated to be causative for them. *DSPP* is bicistronic: dentine sialoprotein (DSP) and dentine phosphoprotein (DPP), the main non-collagenous proteins of dentin extracellular matrix, are cleavage products of its single transcript [48]. Hence, Shields classification reflects in fact a variable expression of the same pathology rather than different entities [49].

Clinically, DGI is characterized by soft blue-brown, translucent teeth (opalescent teeth) (Fig. 8A). Deciduous teeth are usually more severely affected than permanent teeth. The enamel, although apparently unaffected, tends to fracture from the underlying weakened dentin layer, giving a pseudo-AI aspect of teeth. Exposed dentin undergoes rapid attrition leading to shortening of the teeth. Within a single family, the losses by attrition vary from simple erosion to subtotal loss of the crown, the teeth being worn down almost to the gingival level. X-ray aspect is pathognomonic (Fig. 8B): the crowns have a globulous shape, because of an important cervical constriction. Roots are short and thin. The pulp chambers are initially larger than normal pre and immediately post eruption, and then progressively close down to become almost obliterated by abnormal dentin formation. The appearance hence depends upon the age and stage of root development at which the X-Ray is taken (Fig. 8B) [50]. A diagnostic tree is presented in Fig. 9 for non-syndromic dentinogenesis imperfecta.

In DD-II, also called coronal dysplasia, described by Shields (1983) [44], the primary dentition appears opalescent, and on X-rays the pulp chambers are obliterated, resembling to DGI-II. However, unlike DGI, the permanent teeth in DD-II are normal in colour and, on radiographs, have a thistle-tube pulp chamber configuration with pulp stones (Fig. 10) [51,52].

Periapical infections are almost always a problem in DGI, leading to recurrent abscesses [53,54]. The proneness to bacterial infection is possibly due to the bacterial invasion through the dentin tubules communicating with the oral cavity, or to pulp necrosis induced by obliteration. Silva et al. (2004) suggested that dentin matrix proteins could have an active role in
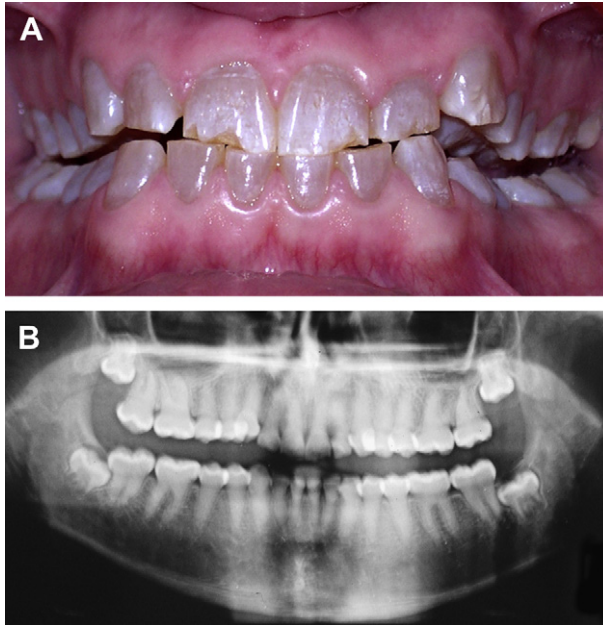
Fig. 8. Dentinogenesis imperfecta, A. oral view, B. Orthopantomogram.

inflammatory cell recruitment during the pathological processes associated with dentin and bone matrix resorption [55,56]. The incidence of dentinogenesis imperfecta is evaluated between 1/6000 and 1/8000 children [14].
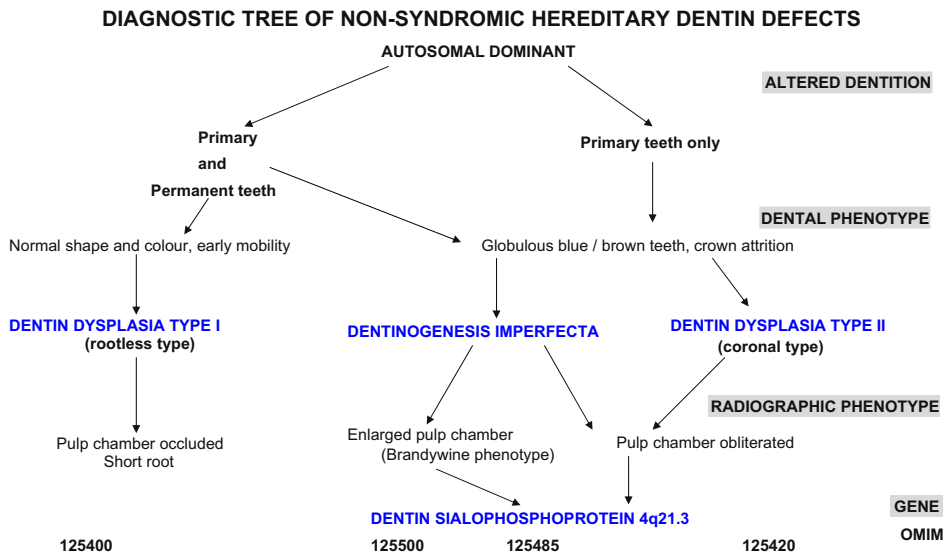

Fig. 9. Diagnostic tree of non-syndromic hereditary dentin defects.

Fig. 10. Dentin dysplasia type II: oral view in mixed dentition.

3.1. DGI type I

This autosomal dominant disorder will be described in part 2. It must be stressed that, clinical and radiological features of DGI type I and DGI type II are identical, and can only be distinguished by the generalized bone undermineralization with susceptibility to fractures that characterizes osteogenesis imperfecta [57].

3.2. DGI type II, type III, and DD type II due to mutations in the DSPP gene

Defects in the human dentin sialophosphoprotein (*DSPP*) gene can cause DGI type II (OMIM 125490) [58–60], DGI type III (OMIM 125500) [61], and DD type II (OMIM 125420) [62]. No mutation in any gene besides *DSPP* has been shown to cause non-syndromic heritable dentin defects.

In Chinese families carrying DGI-II, Xiao et al. (2001) found that the affected individuals also presented progressive sensorineural high-frequency hearing loss (DNF39) [63]. The two *DSPP* mutations in these families affect the transmembrane domain. Mutations of *DSPP* gene, which is bicistronic, encoding both DSP and DPP, are listed in Supplementary Material (Table III).

Fig. 11. Dentin dysplasia type I: orthopantomogram.

DGI type III has been reported in the ''Brandywine isolate'' which is a triracial subpopulation with different clinical manifestations of DGI [64,65]. Teeth present amber discoloration, severe attrition, multiple pulp exposures and, on X rays, a characteristic ''shell teeth'' appearance. In permanent teeth, enamel is pitted and patients have an open-bite. Deciduous teeth have larger than normal pulp chambers. Teeth are less calcified than normal. Some reports have identified obliterated pulp chambers and root canals [66,67]. DGI-III is allelic to DGI-II [61].

Rajpar et al. (2002) reported a missense mutation of *DSPP* in a family with DD-II. The authors hypothesized that this mutation would likely to lead to a loss of function of both dentin sialoprotein and dentin phosphoprotein [62].

3.3. Dentin dysplasia type I (or radicular dentin dysplasia or/rootless tooth)

Both primary and secondary dentitions are affected in DD-I (OMIM 125400). The colour and general morphology of the teeth are usually normal, although they may be slightly opalescent, bluish or brownish. Teeth may be very mobile and exfoliate spontaneously because of inadequate root formation [68]. On radiographs, the roots are abnormally short, or even being absent. Their shape is characteristic, conical [69]. They are cone-shaped, giving them a squat, globular aspect (Fig. 11). The molar frequently present severe taurodontism, corresponding to roots fusion. Pulp chambers as well as root canals are obliterated by dysplastic dentin masses. The pathogenesis of this rare radicular dysplasia and its molecular bases remain uncertain. O'Carroll et al. proposed a subclassification of DD-I based on morphology of roots [69].

4. Genetic anomalies of tooth number

4.1. Tooth agenesis

A tooth is defined to be congenitally missing if it is not erupted in the oral cavity and not visible in a radiograph. Excluding the third molar, the term hypodontia is defined when one to six teeth are missing. Oligodontia (OMIM 604625) is used when more than six teeth are missing and anodontia when there is complete absence of teeth (OMIM 206780). At birth, all primary teeth and first permanent molars crypts are visible by radiograph. Clinical examination at 3- to 4-year old is suitable for diagnosis of congenitally missing primary teeth and at 12- to 14-year old for permanent teeth. Anamnesis to find history of any tooth loss from extraction or trauma and orthopantomogram are recommended for earlier assessment.

Oligodontia is associated with many syndromes, such as the various types of ectodermal dysplasia. In ectodermal dysplasia, the persisting teeth are often small, misshaped, conoid, and usually loose their specific morphology. By contrast, in the disorders discussed under this heading, the shape of the teeth is usually preserved (Fig. 12).

A strong correlation exists between hypodontia in primary and permanent dentitions. Children with hypodontia in the primary dentition nearly always show hypodontia of the successors [70]. Prevalence of oligodontia of primary dentition, ranges from 0.4 to 0.9% in European population [71]. A meta analysis [72] shows that permanent teeth agenesis differs by continent and gender: the prevalence for both sexes was higher in Europe (males 4.6%; females 6.3%) and Australia (males 5.5%; females 7.6%) than for North American Caucasians (males 3.2%; females 4.6%). In addition, the prevalence of dental agenesis in females is 1.37 times higher than in males. The second mandibular premolar is the most affected tooth, followed by the lateral maxillary incisor and the second maxillary premolar (Fig. 13). Unilateral occurrence of

Fig. 12. Non-syndromic oligodontia orthopantomogram.

dental agenesis is more common than bilateral occurrence. However, bilateral agenesis of maxillary lateral incisors is more common than unilateral agenesis. The overall prevalence of agenesis in the maxilla is comparable with that in the mandible, but a marked difference was found between both jaws regarding tooth type. Agenesis of the third molars is the most common, from 23% [73] to 28% [74].

Anodontia or congenital lack of all teeth without associated abnormalities is extremely rare. Some case reports of anodontia [75] have suggested that anodontia of permanent teeth is a homozygote state of the gene responsible for pegged or missing maxillary incisor [76].

Several dental anomalies have been reported together with agenesis: delayed formation and eruption of teeth, ectopic eruption, reduction in tooth size (microdontia) and shape, ectopic maxillary canines, infraposition of primary molar and taurodontism.

Both environmental and genetic factors can cause failure of tooth development. Many environmental factors as irradiation, chemotherapeutic agents [77], or dioxin [78] can arrest tooth development. However, most of the cases are caused by genetic factors [79]. Familial clustering, and higher concordance in monozygotic than in dizygotic twins show the importance of genetic factors. Family studies show that, as an isolated form, both hypodontia and oligodontia may be inherited as an autosomal dominant trait with incomplete penetrance and variable expression [79]. Mesio-distally reduced lateral incisors (or peg-shaped incisors) are associated with agenesis of second premolars [80]. The frequency and inheritance pattern of missing, peg-shaped, and strongly reduced mesio-distally upper lateral incisors in families suggest that they are different expressions of one dominant autosomal gene with reduced penetrance
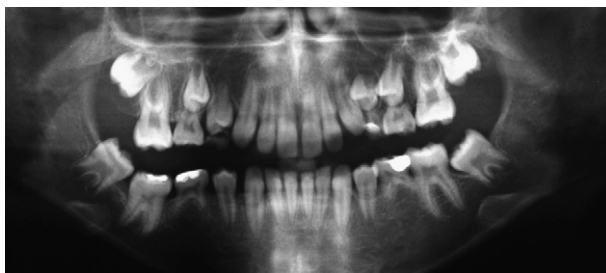

Fig. 13. Congenital agenesis of second premolars at the lower jaw orthopantomogram.

[81]. Sex-linked and polygenic or multifactorial models of inheritance have also been suggested [82]. An autosomal recessive form was shown in one family. The locus was mapped to chromosome 16q12.1 [83]. Specific patterns of hypodontia in families harbouring mutations in homeobox gene might reflect the odontogenic homeobox code proposed by Sharpe [84]. Preceding the initiation of facial development, experiments in rodent identified overlapping spatially restricted areas of homeobox gene expression, designated as ''domains''. They might determine the identity of each individual tooth. *Msx1* and *Msx2* are expressed in the presumptive incisor region, while at the development stage *Barx1*, *Dlx1* and *Dlx2* are coexpressed in the presumptive molar region [85].

4.1.1. Oligodontia with mutations in MSX1 (4p16.1)

Mutations in the homeobox gene *MSX1* lead to specific hypo/oligodontia. Second premolars and third molars are the most commonly affected teeth (OMIM 106600). First maxillary premolars, first mandibular molars, upper lateral incisors and lower central incisor may be absent. Primary dentition is usually normal [86−88].

A nonsense mutation in the *MSX1* gene was associated with tooth agenesis and various combinations of cleft lip and/or palate [89]. Dental phenotypes associated with mutations of *MSX1* are shown in Supplementary Material (Table IV).

4.1.2. Oligodontia with mutations in PAX 9 (14q12−q13)

Mutations in the transcription factor gene, *PAX9*, lead to absence of most permanent molars with or without hypodontia in primary teeth (OMIM 604625) [90]. Some individuals also have missing maxillary and/or mandibular premolars as well as and central mandibular incisors. Smaller teeth observed in affected individuals suggest that *PAX9* is involved not only in the positioning and development of certain teeth but also in the morphogenesis of the entire dentition [91]. There appears to be genotype-phenotype correlations in *PAX9* mutations: missense mutations give a milder phenotype than nonsense and frameshift mutants (see Supplementary Material Table V).

4.1.3. Oligodontia with mutations in AXIN 2 (17q23−24)

Mutations in *AXIN2* cause tooth agenesis and colorectal cancer (OMIM 608615). The patients who carry the mutation lack 8−27 permanent teeth. Penetrance of colorectal cancer is very high. Defects in the deciduous dentition were observed in only one patient [92].

4.1.4. Oligodontia with locus mapped to chromosome 10q11.2

He-Zhao deficiency has been characterized in large Chinese kindred with a distinct form of permanent tooth agenesis (OMIM 61096) [93]. The oligodontia was transmitted in an autosomal dominant fashion with incomplete penetrance. The affected members in the kindred had normal primary dentition, followed by the absence of most permanent teeth, excepted first and/or second permanent molars and central maxillary incisors. The gene locus was mapped to chromosome 10q11.2. *KROX-26/ZNF22* expressed in human tooth development, is a potential candidate gene [94].

5. Supernumerary teeth

Literature reports the prevalence of supernumerary teeth within the mandible and maxilla varying from 0.2 to 0.9% [95]. They may occur in any region of dental arch with a particular

predilection for the maxilla [96]. The presence of single supernumerary tooth associated with the permanent dentition is usually seen in the anterior maxilla [97]. Multiple supernumerary teeth are characteristic of some syndromes. The exact aetiology of supernumerary teeth is still unclear although many theories have been proposed (dichotomy, a part of post permanent dentition…) [98]. Heredity was believed to be an important aetiological factor in the occurrence of supernumerary teeth. Many published cases of supernumerary teeth, such as mesiodens (midline supernumerary tooth), mentioned recurrence within the same family [99−101]. Sedano and Gorlin (1969) indicated the possibility of an autosomal dominant trait with lack of penetrance in some generations [102]. Brook (1984) proposed a combination of genetics and environmental factors to explain the occurrence of supernumerary teeth [103]. Further support of a genetic component in hyperdontia is evidenced by their simultaneous occurrence in monozygotic twins [104]. But actually no mutation was found providing supernumerary tooth.

6. Conclusion

At the present time, the genes responsible for various type of amelogenesis or dentinogenesis imperfecta, oligodontia, and many others disorders affecting the hardness, colour, size, shape and number of teeth are identified. The identification of major genes and the knowledge of their functions, their regulations by local, systemic and environmental factors should provide a clearest understanding of clinical manifestations. Although the teeth are very specialized organs, their determination occurs within the frame of general development, and lead to better diagnosis, preventive approach and treatment. But many of them are involved in syndromic forms lighting the importance of a paediatrician genetic consultation to diagnose syndromic illness.

Appendix A. Supplementary data

Supplementary material associated with this article can be found at doi:10.1016/j.ejmg.2008.02.009.

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