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REVIEW

Isolated dentinogenesis imperfecta and dentin dysplasia: revision of the classification

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Dentinogenesis imperfecta is an autosomal dominant disease characterized by severe hypomineralization of dentin and altered dentin structure. Dentin extra cellular matrix is composed of 90% of collagen type I and 10% of non-collagenous proteins among which dentin sialoprotein (DSP), dentin glycoprotein (DGP) and dentin phosphoprotein (DPP) are crucial in dentinogenesis. These proteins are encoded by a single gene: dentin sialophosphoprotein (DSPP) and undergo several post-translational modifications such as glycosylation and phosphorylation to contribute and to control mineralization. Human mutations of this DSPP gene are responsible for three isolated dentinal diseases classified by Shield in 1973: type II and III dentinogenesis imperfecta and type II dentin dysplasia. Shield classification was based on clinical phenotypes observed in patient. Genetics results show now that these three diseases are a severity variation of the same pathology. So this review aims to revise and to propose a new classification of the isolated forms of DI to simplify diagnosis for practitioners.

INTRODUCTION

Today, molecular biology and genetics studies increase our knowledge about dental germ formation and give a wider view of spatio-temporal patterns of gene expressions and roles. Mutations of these genes explained some of the dental diseases only clinically described before. Structural diseases of mineral tissue may have a primary genetic or a secondary acquired aetiology, with local or general origin. Structural damages diffuse (the whole tooth is affected), extend (all the teeth are affected) and define a hereditary aetiology. A family history of the pathology is often observed, however, sporadic cases may occur.[1]

Dentin genetic diseases are known for several years and many reviews have been published.[2,3] They include two entities: dentinogenesis imperfecta (DGI) and dentin dysplasia (DD).[2,4] The only epidemiological data available was published in 1975. According to Witkop,[5] dentinogenesis imperfecta estimated incidence was between 1/6000 and 1/8000 and dentin dysplasia 1/100 000. These data only came from United States. In other countries, case reports concerned smaller cohorts. Clinical classification used at that time was also old and may be outdated in view of recent information (Shield et al[6]) (Table 1). Shield classified dentinogenesis imperfecta into three subgroups: one associated with a syndrome osteogenesis imperfecta (DGI type I) and two isolated (DGI type II and III); he also described two dentin dysplasia (DD type I and II). In the literature, some case reports described clinical signs that belonged to several of these diseases, so diagnosis and classification were very difficult for practitioners. Therefore, clinical manifestations were insufficient to determine if two pathologies or a differential expression of the same pathology are present. With identification of the key gene of dentinal structure, the dentin sialophosphoprotein (DSPP), authors reported that Shield classification has become obsolete but never proposed a new one.[7] This study proposes to establish a more accurate classification that separates syndromic and isolated forms taking into account the variability of expression because of gene variants.[8]

DENTINOGENESIS AND DENTAL BIOMINERALIZATION

Dentin is a mesenchymal cellular mineralized tissue. Odontoblasts are fully differentiated cells and do not proliferate. The cell bodies are located at the pulp periphery with their odontoblast processes running through dentin to reach enamel dentin junction.[9,10]

Dentin formation consists of odontoblast secretion of an extracellular matrix, the predentin, followed by mineralization. This matrix is composed of 90% of type I collagen and 10% of non-collagenous proteins (NCP) and lipids. NCP regroup: proteins, phosphoproteins, proteoglycans, growths factors, enamel proteins, phosphatases (alkaline phosphatase), proteases (matrix metalloproteinases and their inhibitors: MMPs and TIMPs), that interact and build the scaffold that will support and initiate mineralization.[11]

DSPP encodes for a single mRNA giving three proteins cleaved in specific sites[11,12] by proteases from astacin and MMP families:[9,13] DSP (dentin sialoprotein), DGP (dentin glycoprotein) and DPP (dentin phosphoprotein).[14–17] DSPP-related peptides are the major components of non-collagenous proteins and believed to have a crucial role in converting predentin into mineralized dentin. DSP is a sialic acid-rich proteoglycan with few phosphorylations; conversely, DPP is highly phosphorylated and exhibits numerous isoforms depending on their phosphorylation degree.[16,18] DPP binds to collagen fibrils in specific area (between the gap and overlap zone) of hydroxyapatite nucleation.[19,20] In vitro, immobilized on a stable support and incubated in a solution containing relevant concentration of calcium and phosphate, DPP initiates hydroxyapatite formation at low concentration and inhibits growth at higher concentration.[21] This process adapts mineralization to specific conditions for initiating, height and length growth of hydroxyapatite crystals.[21,22] DPPcKO

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mice analysis revealed that DPP rescues predentin formation compared with Dspp null mice.[23] On the other hand, DSP has still unclear functions but is involved in mineral nucleation.[17,24–26]

The DSPPs are encoded by a 5-exon gene. Exons 2, 3, 4 and the beginning of exon 5 encode for DSP. DGP and DPP are encoded by the end of exon 5. DSPP expression is restricted to differentiated odontoblasts (with transient expression in presecretory ameloblast).[14,27] So, DSPP-related peptides were initially qualified as dentinal-specific proteins. However, later, low levels of DSPP transcripts have been detected in mouse inner ear,[28] periodontal ligament,[29] and bone ($\times$ 400 less).[30,31]

ISOLATED HEREDITARY DENTINAL DISEASES

Dentinogenesis imperfecta (Shield Type II)

The most frequent dentinal disorder is characterized by an autosomal dominant inheritance. The teeth exhibit a grey blue, or amber brown and opalescent discolouration and small height. Enamel is often

Table 1 Former and new classification for isolated dentin rare diseases

OMIM	Shield classification of isolated dentin diseases	Proposed classification of isolated dentin diseases
125400	Dentin dysplasia type I	Radicular dentin dysplasia
		Dentinogenesis imperfecta
125420	Dentin dysplasia type II	Mild form
125490	Dentinogenesis imperfecta type II	Moderate form
125500	Dentinogenesis imperfecta type III	Severe form

dislodged because of altered enamel dentin junction. Consequently, the exposed hypomineralized dentin is fast worn out by attrition. Attrition ranges from few facets of erosion to a complete disappearance of the crown. This influences dental surgery, undertaken frequently on realizing an overdenture in temporary dentition.[32] Primary teeth are often more severely affected than permanent teeth (Figure 1). The radiographical aspect is pathognomonic: bulbous crowns because of an important cervical constriction, short and thick roots and pulp obliteration. Study of the reported cases shows a widest variability: either total or partial obliteration of pulp chamber and/or root whatever dentition concerned.[33,34] Periodontal diseases are frequent without carious disease. Proposed aetiologies are enamel and dentinal permeability for pathological bacteria or necrosis induced by pulpal obliteration. Nevertheless, the interpretation was not satisfactory because it did not take into account the cellular and molecular features of this pathology. Indeed, Silva et al[35] proved that dentin proteins induced neutrophil recruitment under pathology. Histological studies of these teeth showed few and large dentinal tubules running in various directions with atubular area. Enamel fractures occurred along stries of Retzius where prisms are discutinued.[36] Enamel dentin junction is also altered, this explains the phenomenon of enamel chipping. High-resolution synchrotron radiation computed tomography and small angle X-ray scattering showed anomalies of shape and thickness of crystallites.[37]

A candidate gene for DGI-II was identified on chromosome 4q21 by linkage analysis between markers D4S2691 and D4S2692.[38] Xiao et al[28] described the first mutation in association with the disease. The causing gene encodes a structural protein of the dentin, the DSPP, which is involved in mineralization process. This gene belongs to a genes cluster called SIBLING'S (Small Integrin Binding Ligant
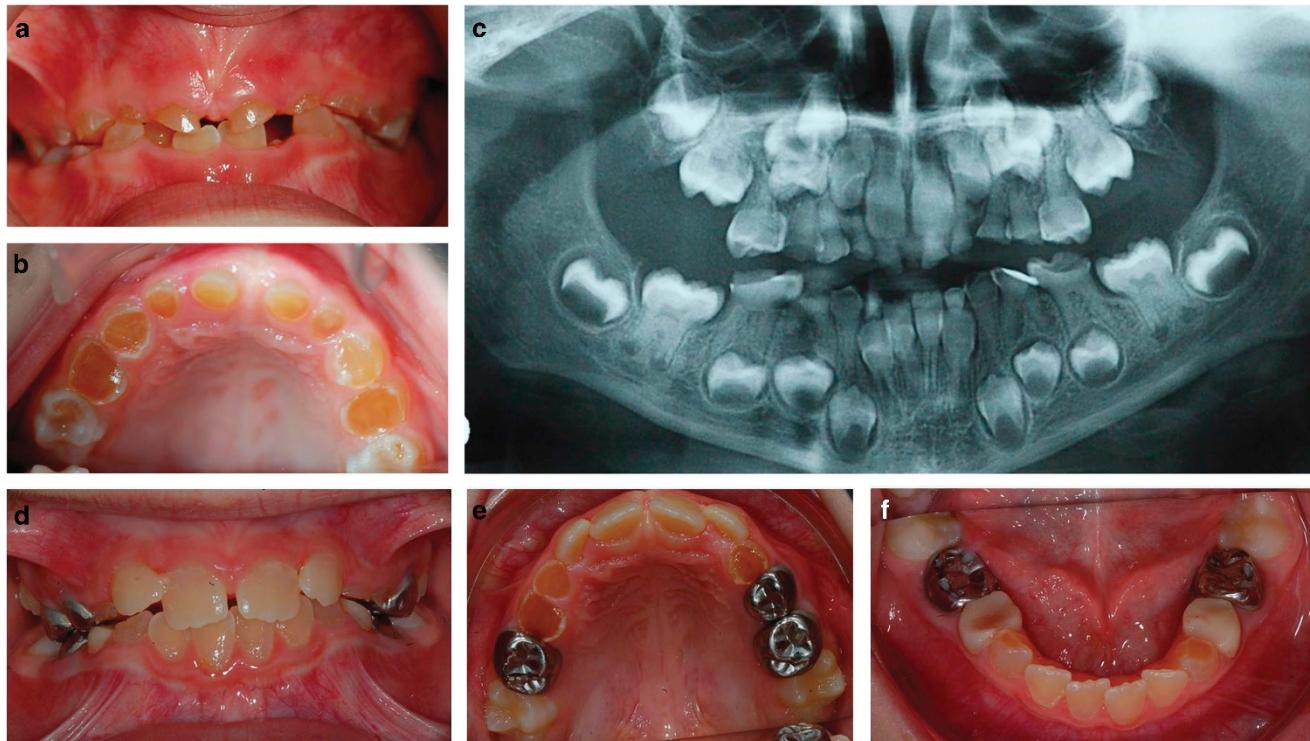
**Figure 1** Clinical phenotype of moderate dentinogenesis imperfecta (formerly DGI Shield type II) in temporary teeth of 6-year-old boy (a–c) and permanent teeth at 8 years old (d–f), primary teeth show brown opalescent discoloration, severe attrition, complete pulp obliteration of erupted teeth, bulbous crown, short root, periapical radiolucency without carie. Temporary teeth are more severely affected than permanent teeth.

N-Linked glycoprotein) implicated in mineralization of dental and bone tissues notably by modulation of matrix metalloproteinases activity.[39]

Dentinogenesis imperfecta (Type III de Shield)

This pathology is very rare, quite exclusively described in the triracial sub-population of Maryland, the 'Brandywine isolate'. This population has the highest incidence of all dental genetic diseases at 1 in 15.[40] Clinically, it is like DGI-II. It affects the two dentitions, with blue amber opalescent teeth, bulbous crowns, and important attrition. But the major difference comes from the pulpal aspect. They were qualified as 'shell teeth' because of an important pulp enlargement on dental X-rays. Pulp is apparent through occlusal dentin and exposures are frequent. The pulpal enlargement results in a reduction in dentin tissue.[41] However, DGI-II and DGI-III could be found on subjects of the same family, and even in the same patient.[42] Dong et al[43] showed a DSPP variant in a Brandiwyne DGI-III family confirming the allelic relation between DGI-II and DGI-III.

Dentin dysplasia type I or radicular

This dentinal defect is extremely rare (1/100 000)[5] and concerns the two dentitions. Clinically, teeth appear normal. The first sign of disease is tooth mobility that leads to premature exfoliations of teeth either spontaneously or with minor traumatisms.[44] Radiographical aspect, classified by O'Carroll et al,[45] is characteristic: roots are shorter (absent in severe cases), merged (taurodont) with an apical conical aspect, with sharp construction (Figure 2). Likewise, premature teeth lost with root length alterations signs this pathology and allow to discriminate DD-I and hypophosphatasia. Pulp is replaced by a mineralized tissue with a dentin aspect: completely or partially with crescent-shaped horizontal radiolucent lines. Periapical lesions are frequent without any other associated pathology. The shorter the root, the more the pulp is obliterated and the greater the prevalence of periodontal pathology.

These teeth were described without colour alterations. However, a careful examination of the literature reveals that this criterion is not

Figure 2 Clinical phenotype of radicular dentinal dysplasia (formerly DD Shield type I): teeth show normal colour (**a**) and shape but roots are severely shortened with conical apex and molar are taurodont (**b**) (arrow).

characteristic. Some authors describe discoloration: brown/blue, yellow/grey,[46,47] or just a brown opacity at the incisal level.[47,48]

This pathology is transmitted as an autosomal dominant trait with complete penetrance.[49] Until now the causing gene is unknown and the physiopathological process not understood. Several hypotheses have been mentioned: an alteration in the epithelial part of tooth germ during root morphogenesis inducing a premature invagination of the Hertwig root sheat and a premature stop.[50,51] Nevertheless, this hypothesis of epithelial alteration is not accepted unanimously. Others implicate the mesenchymal part of teeth, perhaps the problem lies in odontoblast differentiation or functions at the root level.

Dentin dysplasia type II or coronary

DD-II is inherited as an autosomal dominant trait. Clinically, this pathology has the same expression as Shield type II dentinogenesis imperfecta but affects only deciduous teeth. Permanent teeth are normal in colour, shape and height.[52] However, on X-rays, they exhibit a pulp aspect in 'thistle-tube', meaning a large pulpal chamber prolonged by thin root canals (Figure 3). In addition, pulpal stones are frequent.[53,54] DD-II is, therefore, similar to DGI-II and they can be differentiated only by their clinical appearance in permanent teeth. No data concerning DD-II prevalence is reported in the literature, and only few case reports are published. So, we could conclude that this phenotype is very rare. A careful examination of these cases shows that DGI-II is often present in other members of the family related to the patient or in the patient himself with also discoloration of their permanent teeth.[55] An allelic relation between these two pathologies was proposed by McDougall[38] and Dean based on linkage analysis.[56] Description of DSPP mutation in a patient affected by DD-II confirmed this hypothesis and explained these clinical similarities.[57]

Towards a nosology defined by mutations spectrum

To date 38 pathological variants have been described in the DSPP gene, located in the peptide signal region, within the DSP region and within the DPP region (Table 2).[1,7,28,43,57–75] Most of them (28) leads to DGI-II, eight to DD-II and two to DGI-III. No mutation has been described within the DGP coding region. According to many authors, these three pathologies correspond to an expression spectrum of the same physiopathological entity.[2,7,76] Nevertheless, none of them proposed an update of the Shield classification.

To propose a new classification, we analysed the clinical spectrum of DSPP variants related to the disease based on Witkop and Shield diagnosis criteria (Table 2). The analysis of all the reported cases with DSPP variants showed variable expression of the clinical and radiographical features. The crown discoloration was ranged from slight grey, blue-grey, amber to brown. Crowns showed a short and bulbous aspect. Different degrees of attrition ranging from enamel chipping to whole crown disappearance were noted. Finally, roots appeared thinner and shorter. Pulp chamber and root canal obliteration varied from enlargement, partial obliteration with 'thistle-shaped' aspect, narrowed pulp or complete obliteration. Periapical radiolucency may be present or absent. All these diagnosis criteria define a continuum of the phenotypic features from mild, moderate to severe expression (Table 3). Most of the reported cases showed a moderate disease with blue grey amber opalescent teeth, bulbous and short crown, attrition, thinner and shorter roots, and partial or total pulp obliteration. Periapical radiolucency was not constant within the reports. The increased severity of the clinical features in primary teeth when compared with the permanent teeth, usually described in DD-II, DGI-II and DGI-III, was confirmed in all the reviewed cases. Primary teeth showed mainly moderate and severe alterations whereas permanent
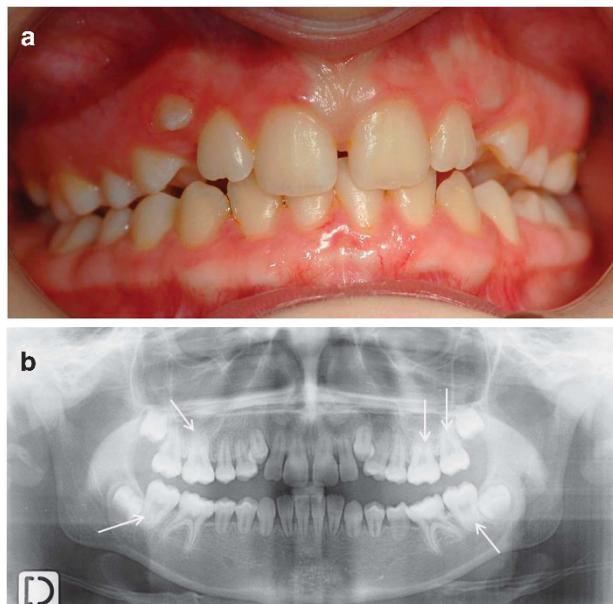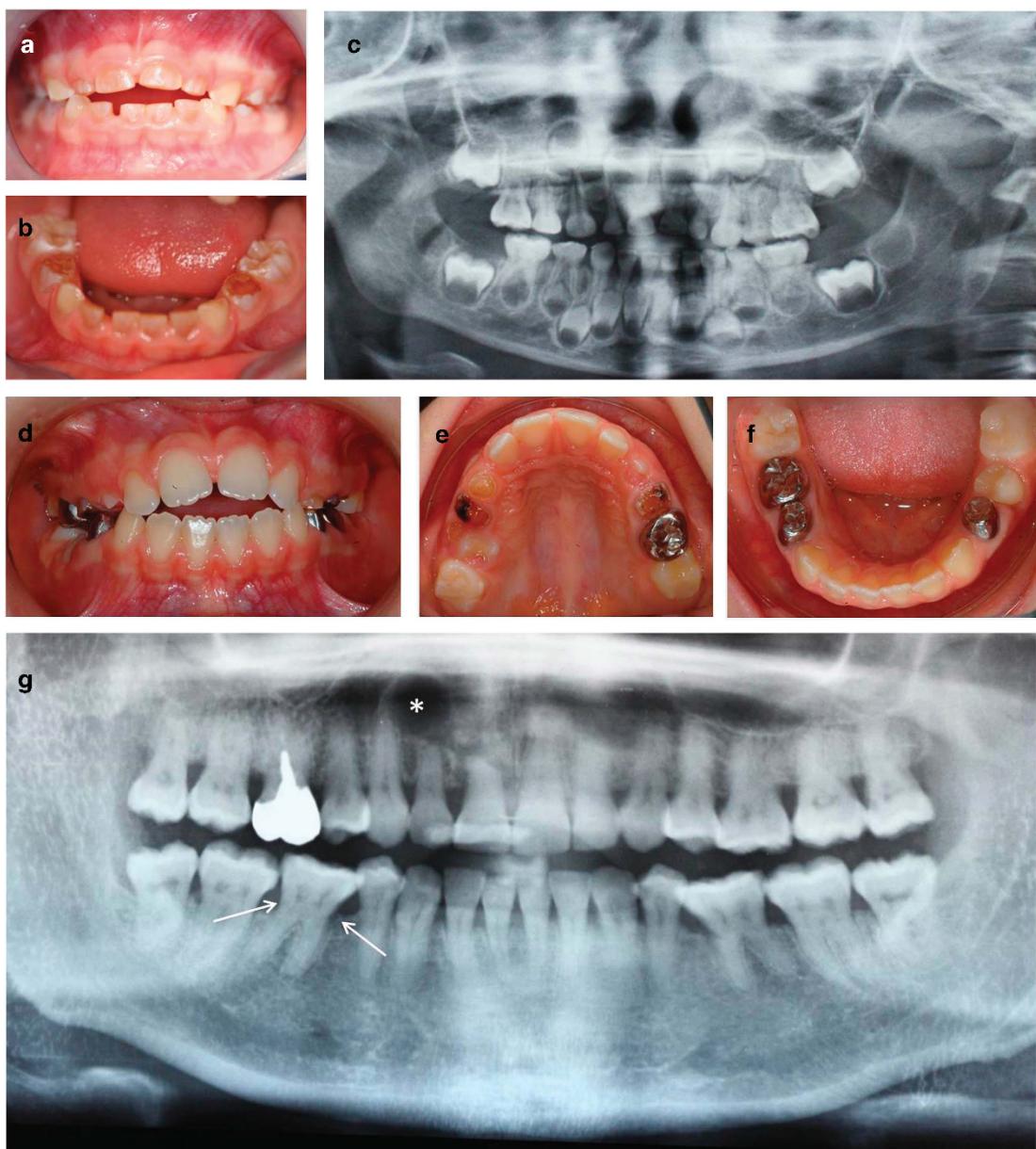
Figure 3 Clinical phenotype of mild dentinogenesis imperfecta (formerly DD Shield type II) in temporary teeth of a 4-year-old girl (**a–c**) and permanent teeth at 10 years old (**d–f**), primary teeth show amber opalescent discoloration, attrition of first molar, partial to complete pulp obliteration of erupted teeth, bulbous crown and short root. Permanent teeth show normal colour without attrition. (**g**) Panoramic radiograph of their mother showing typical 'thistle pulp' aspect, constriction at enamel cement junction (arrow), short root and periapical radiolucency without carie (*).

teeth showed mild to severe alterations. Mild forms were described solely in permanent teeth and defined by the absence or a slight discoloration of teeth, few attrition, and partial pulp obliteration with 'thistle-shaped' aspect. These cases were previously diagnosed as DD-II. DD-II is known to be the less severe phenotype which validated our classification.

Dspp null mice, diagnosed as DGI-III, could be seen as the most severe phenotype of the DSPP disease.[77] Indeed, the mice are characterized by crown discolorations, increased predentin, dentin hypomineralization, severe attrition and shortened teeth roots. Pulp enlargement giving shell teeth aspect was the pathognomonic feature of this phenotype. Enlargement of pulp was described in five cases in primary teeth, and in one patient in permanent teeth. Enlarged pulp in primary teeth in very young children (2–4 years old in all the five

DGI-III cases) has to be carefully considered since it is known that obliteration might progress and permanent denture has to be waited for definitive diagnosis. In permanent teeth, severe phenotype was described in a Brandywine patient diagnosed for DGI-III confirming the proposed classification of severe DI (Table 2).[43] In this case, DNA variant affects the serine repeat and aspartic acid-rich region, especially important to calcium and phosphate interactions that are essential for mineralization. The expression variability, even in the same family, is a constant observation in this hereditary condition. The same DSPP variant could result in a moderate or severe phenotype, previously diagnosed for DG-II or/and DGI-III. Correlating genotype/phenotype is not an easy task if we consider the possible interference of environmental factors. Moreover, in DSPP disease only one gene but three proteins

Table 2 Dental phenotypic analysis of all reported patients affected by DSPP variants

Position	Coding region	dbSNP ID (HGVS)	cDNA	Protein	Primary teeth							Permanent teeth							Shield classification	New DI classification	Reference
					Severity	Crown discoloration	Bulbous and short crown	Attrition	Pulp dystrophy	Periapical pathology	Thin and short root	Severity	Crown discoloration	Bulbous and short crown	Attrition	Pulp dystrophy	Periapical pathology	Thin and short root			
Exon 2 (28_51)	DSP	rs121912988	c.16T>G	p.(F6D)	Moderate	Gray amber	+	NS	PO	NS	NS	Mild / Moderate	Light gray	+	NS	TP / PO	+	NS	DD-II	DI mild	Rajpar et al 2002 [67]
		rs121912989	c.44C>T	p.(A15V)	NS	NS	NS	NS	NS	NS	NS	Moderate	Gray amber	+	NS	PO	NS	+	DGI-II	DI moderate	Malmgren et al 2004 [61]
		rs121912986	c.49C>A	p.(P17T)	Severe	Brown	+	NS	EP	NS	NS	NS	NS	NS	NS	NS	NS	NS	DGI-II	NA	Xiao et al 2001 [28]
		VAR054443	c.49C>T	p.(P17S)	Severe	NS	NS	NS	NS	NS	NS	Moderate	Gray amber	NS	+	PO	NS	+	DGI-II	NA	Zhang et al 2007 [71]
			c.50C>T	p.(P17L)	Severe	Brown	+	+	EP	+	NS	Moderate	Gray amber	+	+	NS	+	+	DGI-II	DI moderate	McKnight et al 2008 [48]
Intron 2			c.52-67>G (IVS2-67>G)	p.(V18_Q45)	NS	Gray amber	+	NS	NS	NS	NS	Mild / Moderate	Absent	NS	+	TP / PO	NS	+/-	DD-I	DI mild-moderate	Lee et al 2013 [66]
			c.52-256df23bp (IVS2-3C>A)		Severe	Brown	+	+	EP	+	NS	Severe	Gray amber	NS	+	NS	NS	NS	DGI-II	DI moderate	Wang et al 2009 [65]
			c.52-3C>G (IVS2-3C>G)		Severe	Brown	+	+	EP	+	NS	Severe	Gray amber	+	+	NS	+	NS	DGI-II	DI moderate	Kim et al 2004 [74]
			c.52-3C>A		Moderate	Gray amber	+	+	PO	NS	+	Moderate	Gray amber	+	+	PO	NS	+	DGI-II	DI moderate	Holappa et al 2006 [38]
Exon 3 (52_135)		rs121912987	c.52G>T	p.(V18F)	NS	Brown	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	DGI-I	NA	Xiao et al 2001 [28]
					Severe	Brown	+	+	EP	-	+	NS	Gray amber	NS	+	NS	+	NS	DGI-I/DGI-II	NA	Kim et al 2005 [61]
					Severe	Brown	+	+	EP	NS	+	Moderate	Gray amber	+	+	PO	+	NS	DGI-II	DI moderate	Song et al 2006 [70]
					Moderate	Gray amber	+	+	PO / EP	+	NS	Moderate	Brown	+	+	NS	+	+	DGI-I/DGI-II	DI moderate	Holappa et al 2006 [38]
			c.53T>A	p.(V18D)	Moderate / severe	Brown	+	+	EP	NS	+	Moderate / severe	Brown	+	+	NS	NS	NS	DGI-II	DI moderate-severe	Lee et al 2009 [64]
					Moderate	Brown	+	+	PO	NS	NS	Moderate	Gray amber	+	+	PO	+	+	DGI-II	DI moderate	Kida et al 2009 [60]
		rs121912985	c.133C>T	p.(Q45*)	Moderate	Brown	+	+	PO	NS	NS	Moderate	Gray amber	+	+	PO	NS	NS	DGI-II	DI moderate-severe	Lee et al 2011 [64]
Intron 3			c.135+1G>A		NS	NS	NS	NS	PO	NS	NS	NS	Gray amber	NS	NS	PO	NS	NS	DGI-II	DI moderate	Zhang et al 2001 [72]
			c.135+1G>T		NS	NS	NS	NS	PO	NS	NS	NS	NS	NS	NS	NS	+	NS	DGI-II	NA	Xiao et al 2001 [28]
			c.135+2T>C		NS	NS	NS	NS	PO	NS	+	NS	NS	NS	NS	NS	NS	NS	DGI-II	NA	McKnight et al 2008 [48]
			c.135+3A>G (IVS3+3A>G)		Moderate	Brown	+	NS	PO	-	+	Moderate	Brown	+	+	NS	+	+	DGI-II	DI moderate	Zhang et al 2011 [71]
Exon 4 (136_1122)		rs36094464	c.202A>T	p.(R68W)	NS	NS	NS	NS	PO	NS	-	NS	Gray amber / Brown	-	-	PO	-	NS	DGI-II	DI moderate	Bai et al 2010 [58]
			c.1686delT	p.(D562Efs*752)	Moderate	Gray amber	NS	NS	NS	NS	NS	Moderate	Brown	+	+	PO	NS	+	DGI-II	DI moderate	Malmgren et al 2004 [61]
			c.1830delC	p.(S610Rfs*704)	Moderate	Brown	-	+	EP	NS	NS	Moderate	Gray amber	-	+	TP	NS	+	DGI-II	DI moderate-severe	Holappa et al 2006 [38]
	DPP		c.1870_1873delTCAG	p.(S624Tfs*687)	Moderate	Gray amber	+	+	PO	NS	+	Moderate	Absent	-	-	TP	NS	NS	DD-II	DI mild	Niemien et al 2011 [63]
			c.1918_1921delTCAG	p.(S640Tfs*671)	NS	Brown	+	NS	PO	NS	NS	NS	Absent	NS	NS	NS	+	NS	DD-II	DI mild-moderate	McKnight et al 2008 [48]
			c.1922_1925delACAG	p.(D641Afs*672)	Moderate	Brown	-	+	PO	NS	NS	Mild / Moderate	Absent	-	+/-	TP / PO	NS	+/-	DD-II	DI mild-moderate	Niemien et al 2011 [63]
			c.2040delC	p.(S680fs*1313)	Moderate	Brown	+	+	PO	NS	NS	Mild / Moderate	Absent	-	+	TP / PO	NS	+	DGI-II	DI mild-moderate	Song et al 2008 [70]
			c.2063delA	p.(D680KVfs*26)	Moderate	Brown	+	+	PO	NS	NS	Moderate	Light gray	+	NS	TP / PO	NS	+/-	DGI-II	DI moderate	Niemien et al 2011 [63]
			c.2272delA	p.(S758Afs*554)	NS	NS	NS	NS	NS	NS	NS	Moderate	Light gray	+	NS	TP	+	NS	DGI-II	DI mild	McKnight et al 2008 [48]
			c.2349delT	p.(S783Rfs*531)	Moderate	Gray amber	+	+	NS	NS	NS	Moderate	Gray amber	+	+	PO	+	NS	DGI-II	DI moderate	Niemien et al 2011 [63]
			c.2525delG	p.(S842Tfs*471)	NS	NS	+	-	PO	NS	NS	Moderate	Gray amber	+	-	PO	NS	NS	DGI-II	DI moderate	McKnight et al 2008 [48]
Exon 5 (1123_4211)			c.2593delA	p.(S865fs*1313)	NS	NS	NS	NS	PO	NS	NS	NS	Gray amber	NS	NS	NS	+	NS	DGI-II	NA	Song et al 2008 [70]
			c.2684delG	p.(S889Tfs*425)	Moderate	Brown	+	NS	PO	NS	NS	Moderate	Brown	NS	+	PO	NS	NS	DGI-II	DI moderate	Niemien et al 2011 [63]
			c.2688delT	p.(S895fs*1313)	Moderate	Brown	+	NS	PO	+	NS	Moderate	Gray amber	NS	NS	PO	NS	NS	DGI-II	DI moderate	Song et al 2008 [70]
			c.3416delC		Moderate	Brown	+	NS	PO	-	NS	Moderate	Gray amber	+	NS	TP / PO	NS	+	DGI-II	DI mild-moderate	Lee et al 2011 [64]
			c.3438delC	p.(D1146fs*1313)	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	DGI-II	NA	McKnight et al 2008 [48]
			c.3546_3558delTAGCAfnsG	p.(D1182fs*1312)	NS	NS	NS	NS	PO	NS	NS	Moderate	Light gray	+	NS	PO	-	NS	DGI-II	DI moderate	Song et al 2008 [70]
			c.3500delG		NS	NS	NS	NS	NS	NS	NS	Moderate	Light amber	+	NS	PO	-	NS	DGI-II	DI moderate	Lee et al 2011 [64]
			c.3582_3591del CAGCAGCGAT GAC AGC, c.3599_3634del GT GAC AGC AGT GAC AGC AGC GAC AGC AGT GAC AGC A and c.3715_3716ins GC GAT AGC AGT GAC AGC A	p.(Del1160_1171505505505505 and Ins1198_1199505505)	Moderate	Gray amber	+	NS	PO	+/-	NS	Moderate	Brown	+	+/-	TP / PO	+	+	DGI-II	DI mild-moderate	Niemien et al 2011 [63]
			c.3625_3700del 76bp		Severe	Brown	+	NS	EP	NS	NS	Severe	Brown	+	+	EP	NS	NS	DGI-II	DI severe	Dong et al 2005 [59]
					NS	NS	NS	NS	NS	NS	NS	Moderate	Gray amber	+	+	TP / PO	+	+	DGI-II	DI mild-moderate	Niemien et al 2011 [63]

NS = Not Shown
+ = Present
- = Absent
Ref NM_014208.3

PO = partial or complete pulp obliteration
TP = thistle shaped pulp
EP= enlarged pulp

NA = Not Applicable because lack of data

All variants can be consulted on the LOVD website (http://www.lovd.nl/DSPP).

Table 3 Variability expression of clinical and radiographic signs in dentinogenesis imperfecta ranged from mild to severe affection

	Dental phenotype variability of DI criterias		
	Mild severity	Moderate severity	Severe
Crown discoloration	Normal, light grey	Blue grey amber opalecent	Brown opalecent
Crown dysmorphology		Bulbous (increased constriction at CEJ) and short crown	
Attrition		Increased severity from enamel chipping to whole crown disappaerance	
Pulp obliteration	Partial obliteration with 'thistle-shaped' appearance	Narrowed pulp to complete obliteration	Enlarge pulp with 'shell teeth' appearance
Thin and short root		Increased severity	
Periapical pathology		Increased severity with number	

are in cause. Differential functions and levels of expression (DSP to DPP molar ratio 1:10)[78] of each protein complicate the interpretation of the findings.

The present analysis revealed that DSPP-related disease showed variable expression severity of the same entity. We propose that all DSPP diseases are called exclusively 'Dentinogenesis Imperfecta (DI)' characterized by grey to brown crowns, shortened and bulbous crowns, shorter and thinner roots, attrition and pulp alterations. The severity can be ranged from mild to severe forms. Mild forms are characterized by no or very few signs in permanent teeth except 'thisthle like' aspect of pulp and a moderate affection of primary teeth. Severe forms are characterized by the presence of all DI features with pulp enlargement especially in permanent teeth.

This present analysis simplifies dentinogenesis imperfecta diagnosis taking account the clinical variability and may really help practitioners. Shield type II dentin dysplasia may be considered as a mild form and Shield type III dentinogenesis imperfecta as a severe form of DI (Table 1). (Of course, Shield DGI-I, which is syndromic, also called osteogenesis imperfecta is not concerned by this new classification since it is a whole different pathology). Dentin dysplasia Shield type I becomes the unique radicular pathology named radicular dentin dysplasia. Its aetiology is still unknown.

CONCLUSION

Dentin gene diseases are since long described in the literature from the clinical viewpoint. Like many hereditary pathologies, they are very rare, but according to Witkop,[40] they occur more often than enamel diseases. A large revision about all of these epidemiological data would give us new data about this observation that concerned only US population, in 1970. Still now, isolated dentinal genetical diseases regroup four entities among which three look like each other clinically. Molecular genetics studies allow to discriminate only two pathologies: dentinogenesis imperfecta (formerly DGI Shield type II, III and DD Shield type II) and dentin dysplasia (formerly DD Shield type I) that correspond to a radicular anomaly. After syndromic exclusion (no bone alteration especially), isolated dentinogenesis imperfecta should actually be regarded as a single entity with an important variability of expression following our new classification. This disease is caused by the DSPP gene variants, encoding the major non-collagenous proteins, which are implicated in initiation and growth of hydroxyapatite crystals. Radicular dentin dysplasia aetiology and physiopathology are still obscure.

All variants published and presented in Table 2 can be consulted on the LOVD website (http://www.lovd.nl/DSPP).

ABBREVIATIONS

DSPP, Dentin sialophosphoprotein; DSP, Dentin sialoprotein; DPP, Dentin phosphoprotein; DGP, Dentin glycoprotein; DGI/DI, dentinogenesis imperfecta; DD, dentin dysplasia; MM, Pmatrix metaloproteinase; NCP, non-collagenous protein; TIMP, tissue inhibitor metalloproteinase; SIBLING'S, Small Integrin Binding Ligant N-Linked glycoprotein.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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