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Disorders of Human Dentin

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Abstract

Dentin, the most abundant tissue in teeth, is produced by odontoblasts, which differentiate from mesenchymal cells of the dental papilla. Dentinogenesis is a highly controlled process that results in the conversion of unmineralized predentin to mineralized dentin. By weight, 70% of the dentin matrix is mineralized, while the organic phase accounts for 20% and water constitutes the remaining 10%. Type I collagen is the primary component (>85%) of the organic portion of dentin. The non-collagenous part of the organic matrix is composed of various proteins, with dentin phosphoprotein predominating, accounting for about 50% of the non-collagenous part. Dentin defects are broadly classified into two major types: dentinogenesis imperfectas (DIs, types I–III) and dentin dysplasias (DDs, types I and II). To date, mutations in *DSPP* have been found to underlie the dentin disorders DI types II and III and DD type II. With the elucidation of the underlying genetic mechanisms has come the realization that the clinical characteristics associated with *DSPP* mutations appear to represent a continuum of phenotypes. Thus, these disorders should likely be called *DSPP*-associated dentin defects, with DD type II representing the mild end of the phenotypic spectrum and DI type III representing the severe end.

Keywords

Dentin; Dentin dysplasia; Dentinogenesis imperfecta; DSPP; Small integrin-binding ligand N-linked glycoprotein

Introduction

Dentin defects are broadly classified into two major types: dentinogenesis imperfectas (DIs, types I–III) and dentin dysplasias (DDs, types I and II). This classification originally proposed in 1973 was based solely upon clinical characteristics and radiographic features without knowledge of the underlying molecular pathophysiology [Shields et al., 1973].

Inheritance of dentin defects is typically autosomal dominant, although autosomal recessive and X-linked cases of dentin defects associated with syndromic conditions are reported.

Dentin defects occur as a feature in a number of syndromes, including osteogenesis

imperfecta [Steiner et al., 2005], Ehlers-Danlos syndrome (EDS) [De Coster et al., 2007], tumoral calcinosis [Benet-Pagès et al., 2005; Ichikawa et al., 2005; Specktor et al., 2006] and hypophosphatemic rickets [Qin et al., 2004] as well as potentially newly described syndromes [Cauwels et al., 2005; De Coster et al., 2006]. Clinical features associated with DI and DD include brown-blue or opalescent brown appearance of teeth. Enamel fractures off of the dentin, facilitating attrition of dentin. Radiographically, crowns appear bulbous, pulp chambers are small or obliterated and roots may be narrow with small or obliterated canals. Both primary and secondary teeth may be affected. As the underlying genetic defects are being identified, it is now evident that variable expressivity accounts for some of the differences in clinical expression.

Dentinogenesis

Dentin, the most abundant tissue in teeth, is produced by odontoblasts, which differentiate from mesenchymal cells of the dental papilla, and forms the foundation for enamel formation [Arana-Chavez and Massa, 2004]. Dentinogenesis is a highly controlled process that results in the conversion of unmineralized predentin to mineralized dentin. Dentin is heavily mineralized (70% of the matrix by weight) with the organic phase accounting for 20% of the matrix, and the remaining 10% being water [Rajpar et al., 2002]. Type I collagen is the primary component of the organic portion of dentin, accounting for over 85% of the organic phase. The non-collagenous part of the organic matrix is composed of various proteins, with dentin phosphoprotein (DPP) predominating, accounting for about 50% of the non-collagenous part.

Odontoblasts differentiate during the crown formation stage of tooth development. The mature odontoblasts line the pulp chamber as a layer of single cells and secrete an organic matrix into the surrounding space. Predentin is an unmineralized zone of 10–40 µm that separates the mineralized dentin and the odontoblasts. The odontoblasts secrete type I collagen into the predentin layer where the collagen molecules aggregate into fibrils. At the same time, Ca²⁺ ions are brought to the mineralization front along with various proteins, such as DPP and dentin sialoprotein (DSP). DPP then serves as a nucleator of mineralization and induces apatite formation. As they secrete the organic matrix, the odontoblasts migrate towards the center of the dental papilla, elongating as they migrate, leaving cytoplasmic extensions, known as the odontoblast process. This section of mineralized tissue is called mantle dentin and is typically 150 µm thick. Primary dentin forms as the odontoblasts increase in size and secrete collagen in smaller quantities. The smaller extracellular space results in more tightly packed collagen fibrils that are then mineralized. After completion of root formation, secondary dentin is formed, but the rate of formation is slower than that of primary dentin and not uniform across the tooth. Tertiary dentin is synthesized in response to external stimuli such as caries or trauma. Histologically dentin is permeated by dentinal tubules that run from the pulpal wall to the dentino-enamel junction. The diameter of the tubules is 3.0 µm at the pulpal wall, but only 0.06 µm at the dentino-enamel junction. These tubules contain odontoblastic processes and dentinal fluid, which contains a variety of proteins including transferrin, tenascin, albumin and proteoglycans [Linde and Goldberg, 1993].

Dentinogenesis Imperfecta

In DI, both the deciduous and permanent teeth are clinically affected, appearing blue-gray or amber brown and opalescent, although the deciduous teeth are often more severely affected. Radiographically, bulbous crowns, narrow roots, and small or obliterated pulp chambers and root canals are seen. Histologically, the dentin has a dysplastic appearance with irregular dentinal tubules and areas lacking dentin tubules. Because of the defect in dentin, enamel is easily broken off, exposing the underlying dentin, leading to accelerated attrition. Three subtypes of DI have been recognized (table 1; fig. 1).

DI Type I

Individuals with DI type I have a syndromic form of DI. In addition to having DI, they also have osteogenesis imperfecta (OI), an autosomal dominant disorder of bone fragility. OI is further classified into collagenous and non-collagenous forms. All four collagenous OI subtypes can have DI as a feature. DI is more common in types III and IV. DI only occurs in cases of OI due to dominant negative effects (such as missense mutations). In some cases, DI may be the most penetrant clinical finding [Pallos et al., 2001]. Thus, it is important for health care providers to ask about histories of bone fractures (especially with minimal trauma), joint hyperextensibility, short stature, hearing loss and scleral hue in all patients exhibiting DI. Approximately 90% of individuals with OI types I–IV have an identifiable mutation in *COL1A1* or *COL1A2*, the two genes that encode the chains of type I procollagen [Steiner et al., 2005].

DI Type II

The presence of DI without other etiologically related clinical findings (i.e. non-syndromic DI) is classified as DI type II. The clinical and radiographic tooth phenotype is indistinguishable from that seen in syndromic DI type I. Penetrance is almost complete and de novo mutations are rare. The estimated incidence of DI type II is between 1/6,000 and 1/8,000 [Witkop, 1957]. A few families with DI type II have also had hearing loss, but it is not clear how the mutation in *DSPP* causes the hearing loss.

DI Type III

DI type III (OMIM 125500) was initially described in the Brandywine, triracial isolate in southern Maryland. The phenotype in this extended kindred can be traced to a sea captain from Liverpool who came to Maryland in 1732 [Witkop, 1965]. This isolate has the highest reported frequency of dental defects in the world, with approximately 6% having DI [Kim et al., 2005]. Overall, 1 in 15 individuals in this population is estimated to have DI [Witkop, 1957]. In addition to the abnormalities in tooth color and size seen in DI type II, very large pulp chambers and multiple pulp exposures are seen in deciduous teeth in approximately 2% of the Brandywine cohort. Enamel pitting has also been reported in some members of the Brandywine cohort [Levin et al., 1983]. These large pulp chambers led to the designation DI type III, however not all affected family members demonstrate large pulp chambers. Other unrelated families have been reported with these clinical features, demonstrating that the features associated with DI type III are not unique to the Brandywine cohort, and may represent variable clinical expression. Asymptomatic radiolucencies are sometimes seen in

teeth with significant attrition. The Brandywine cohort also segregated juvenile periodontitis as an autosomal dominant trait [Boughman et al., 1986]. Linkage analysis supported the existence of a separate gene for juvenile periodontitis, located approximately 17 cM from the locus for DI type III.

Dentin Dysplasia

In DD, the permanent teeth are typically normal in color, but the pulp chambers are obliterated by abnormal dentin.

DD Type I

DD type I (OMIM 125400) is the rarest of the human dentin disorders, with an estimated incidence of 1 in 100,000. In DD type I, the crowns of deciduous and permanent teeth are normal in shape, form and color, but have short roots with high mobility leading to early exfoliation; frequent periapical radiolucencies are also noted.

DD Type II

In DD type II (OMIM 125420), the deciduous teeth have features of DI type II, but the permanent teeth appear normal. Radiographically, pulp cavities show thistle-tube deformity and commonly have pulp stones. Unlike DD type I, root length is normal and frequent periapical radiolucencies are not observed.

Genes Involved in Dentin Formation

COL1A1 and COL1A2

Type I collagen, which comprises the bulk of the organic phase of dentin, is a triple helix containing two $\alpha 1(I)$ and one $\alpha 2(I)$ chain. The two chains are encoded by the *COL1A1* and *COL1A2* loci, at 17q21.3-q22 and 7q22.1, respectively. Assembly of the collagen triple helix begins at the C-terminus and proceeds towards the N-terminus. Thus mutations at the C-terminus are typically associated with a more severe phenotype than those nearer the N-terminus [Steiner et al., 2005]. OI type I usually results from mutations in *COL1A1* that result in haplosufficiency of the $\alpha 1(I)$ chain. Haploinsufficiency leads to half of the amount of type I collagen. No abnormal collagen is produced. These individuals do not have DI. Individuals with OI type I with DI (OI type IB in the classification of Sillence et al. [1979]) have missense mutations in *COL1A1*. A missense mutation is a nucleotide substitution in the coding region of a gene that changes a nucleotide codon so that it codes for a different amino acid in the protein, resulting in an abnormal collagen fibril. Incorporation of an abnormal collagen fibril interferes with normal triple helical formation and produces OI through a dominant negative effect. In this case, three fourths of the collagen produced are abnormal. Missense mutations also underlie OI types II, III, and IV. The ultimate phenotype depends upon the particular substitution, with substitutions of glycine in the $\alpha 1(I)$ chain by arginine, valine, glutamic acid, aspartic acid, and tryptophan usually resulting in OI type II if they occur in the carboxylterminal 70% of the triple helix. DI may or may not be present in these cases of OI due to dominant negative effects. Recently, a patient with type I EDS, a disorder characterized by joint hypermobility,

skin hyperextensibility and tissue fragility, in whom a C to T transition (c.934C>T; p.R134C) in *COL1A1* was identified, was shown to have structural dentin defects despite a clinically unaffected dentition [De Coster et al., 2007]. This same mutation has been reported in 2 additional type I EDS patients, but no histological and ultra-structural studies have been performed on teeth from those patients [Nuytinck et al., 2000].

SIBLINGS

The SIBLING (small integrin-binding ligand N-linked glycoprotein) family of proteins includes dentin sialophosphoprotein (DSPP), osteopontin [also known as SPP1 (secreted phosphoprotein)], IBSP (integrin binding sialoprotein), DMP1 (dentin matrix protein 1), and MEPE (matrix extracellular phosphoglycoprotein) [Fisher et al., 2001]. Although all members were originally isolated from tooth or bone, it is now apparent that at least some SIBLINGS are expressed in non-mineralized tissues. The SIBLING genes are syntenic (on the same chromosome), clustered in a 0.37-Mb region on chromosome 4q. The encoded proteins contain an integrin binding tripeptide (Arg-Gly-Asp) and several conserved N-glycosylation and phosphorylation sites. The expression levels of the different SIBLINGS vary greatly between tissues. For example, OPN is expressed in bone at a level 70 times higher than that in dentin [Butler et al., 2003]. Although all SIBLINGS are thought to function in the mineralization process, their expression outside of mineralized tissues suggests additional roles. The recent finding of DSPP expression in embryonic kidney and lung has led to the hypothesis that DSPP may regulate branching morphogenesis [Alvares et al., 2006]. The only two SIBLINGS known to be associated with human genetic disorders are *DMP1* and *DSPP*. Mutations in *DMP1* were recently shown to underlie autosomal recessive hypophosphatemic rickets [Feng et al., 2006; Lorenz-Depiereux et al., 2006].

DSPP

DSPP is located at 4q22.1 and consists of five exons spanning 8,343 bp. DSPP is expressed in dentin at levels that are hundreds of times higher than that of other tissues. Three distinct protein products result from proteolytic cleavage of the initial 1253-amino acid protein product, DSPP: DSP (amino acids 16–374), dentin glycoprotein (DGP; amino acids 375–462), and DPP (amino acids 463–1253; fig. 2). The initial cleavage by a yet unidentified protease releases DPP, a process that occurs almost immediately upon formation of DSPP [Yamakoshi et al., 2006]. Matrix metalloproteinase (MMP) 20 then cleaves DSP-DGP to generate DSP and DGP, while MMP2 catalyzes other cleavages on DSP. DPP is a highly repetitive protein with a great degree of phosphorylation and is thought to be involved in the nucleation and control of mineralization in dentin [George et al., 1996]. DPP contains repeats of aspartic acid (Asp) and phosphoserine (Pse) mainly as (Asp-Pse-Pse) and (Asp-Pse). There is extensive variability in the number of repeats in normal individuals [Fisher, pers. commun.]. After synthesis and cleavage, DPP moves quickly to the mineralization front and binds to collagen. DSP is a heavily glycosylated protein that forms covalent dimers by intermolecular disulfide bridges [Yamakoshi et al., 2005], but whose function is not entirely known. DGP was recently isolated from porcine odontoblasts and found to contain four phosphorylated serines and one N-glycosylated asparagine. Given the posttranslational modifications and amino acid conservation across species, it has been proposed that DGP plays a role in dentin biomineralization [Yamakoshi et al., 2005].

DSPP knockout mice develop abnormalities similar to those seen in DI type III [Sreenath et al., 2003]. Histologically, large areas of unmineralized dentin were seen as well as an irregular border between the unmineralized and mineralized dentin. In addition, there were areas of partially mineralized dentin between areas that were fully mineralized.

To date only mutations in *DSPP* have been found to underlie DI types II and III and DD type II. Although 11 mutations have been reported in the literature, two of the published disease-causing mutations are actually normal sequence variants: p.R68W and Del1160–1171; ins1198–1199 (table 2). Holappa et al. [2006] found the p.R68W change in 15% of Finnish controls. Our laboratory found p.R68W with allele frequencies of 6 and 16% in Caucasian and African-American controls, respectively. We have also studied a branch of the Brandywine family reported by Dong et al. [2005]. Although we identify the same alteration in the hypervariable region, there is considerable variation in this region in normal controls, with similar deletions and insertions found. This normal variation is apparent when trying to align the genomic sequence with the DSPP cDNA reference sequence [Beattie et al., 2006]. We identified a second nucleotide change in the genomic sequence (g.49C>T) of the *DSPP* gene in this family, predicted to result in a p.P17S missense alteration, that segregates with the phenotype and causes endoplasmic reticulum retention of the protein in a functional assay. Thus, we propose that the p.P17S substitution is the true causative mutation in the Brandywine family. Of the nine confirmed *DSPP* mutations, all occur within the DSP region of DSPP. It should be pointed out that the effect of the mutation on the protein is simply a prediction, as more than one consequence may be possible. For example, the c.52G>T alteration might result in the missense alteration, p.V18F. On the other hand, this alteration occurs as the first nucleotide of exon 3 and may thus disrupt splicing, causing skipping of exon 3 (p.V18_Q45del). Site-directed mutagenesis was used to introduce each of the nine mutations and the p.R68W polymorphism into the human DSP mRNA which were then transfected into odontoblast cells. The ability of the cells to secrete DSP was evaluated by Western blot analysis. This functional assay demonstrated that with the exception of the nonsense mutation, p.Q45X, all other mutations are associated with endoplasmic reticulum retention, consistent with a dominant negative mutation [Choi et al., submitted].

The finding that the same mutation produces different phenotypes suggests that factors other than the specific *DSPP* mutation contribute to the ultimate phenotype. There are some families with dentin defects linked to 4q22.1 in which no *DSPP* mutation can be identified [Beattie et al., 2006]. Family A in the paper by Malmgren et al. [2004] is also an example of linkage to 4q22.1 without the underlying defect identified since the predicted causative mutation (p.R68W) has since been shown to be simply a non-synonymous single nucleotide polymorphism that segregated with the phenotype. Whether these families have undetected mutations in *DSPP*, e.g. intronic changes, promoter alterations, deletions of exons, or mutations in the hypervariable region which is typically not analyzed, or have involvement of another gene in the 4q22.1 region remains to be determined.

Proteases

As noted above, MMP2 and MMP20 were recently shown to be involved in the processing of DSPP [Yamakoshi et al., 2006], specifically to generate DSP and DGP. Mutations in *MMP20* result in amelogenesis imperfecta without an obvious dentin abnormality [Kim et al., 2005; Ozdemir et al., 2005]. It has been suggested that molecular redundancy may explain this lack of phenotype [Yamakoshi et al., 2006]. MMP8 was recently identified as the major collagenase in human dentin [Sulkala et al., 2007]. Other metalloproteases synthesized by odontoblasts include MMP9, and membrane-bound MMP14 (MT1-MMP). KLK4 has also been detected in dentin extracts but its role in processing dentinal proteins is not known [Yamakoshi et al., 2006], but its expression by odontoblasts might be associated with the hypermineralization of enamel above the dentino enamel junction [Fukae et al., 2002].

Other Genes Expressed in Dentin

A variety of other genes are expressed in dentin. Many of these genes, if mutated, would not be expected to give rise to isolated enamel defects. Patients with EDS type VIIC, who have a defect in the *ADAMTS2* gene which encodes the enzyme responsible for removing the N-terminal propeptide in procollagen types I–III, exhibit dentin defects [De Coster et al., 2006]. Recently, HMGB1 (high mobility group box 1) was shown to be highly expressed in dentin at regions undergoing mineralization [Sugars et al., 2007]. HMGB1^{−/−} mice die within 24 h of birth due to hypoglycemia [Calogero et al., 1999]. *PHEX*, mutated in X-linked hypophosphatemic rickets (XLH), encodes an endopeptidase postulated to play a role in the processing of DMP1 and DSPP [Qin et al., 2004]. Loss of function mutations in the gene encoding fibroblast growth factor 23 (*FGF23*), a phosphaturic protein, result in autosomal recessive hyperphosphatemic familial tumoral calcinosis (OMIM 211900) [Benet-Pagès et al., 2005] while gain of function mutations produce autosomal dominant hypophosphatemic rickets (OMIM 193100) [ADHR Consortium, 2000]. Hyperphosphatemic familial tumoral calcinosis can also result from mutations in *GALNT3* which encodes a glycosyltransferase involved in initiating O-glycosylation [Ichikawa et al., 2005; Specktor et al., 2006]. The demonstration that both hyper- and hypophosphatemic disorders have dentin defects underlies the importance of phosphate homeostasis in normal dentin development.

Proposal for New Classification of Dentin Defects

The finding of differing dentin phenotypes within a family highlights the variable expressivity often associated with autosomal dominant disorders. The clinical phenotypes associated with *DSPP* mutations appear to represent a continuum of phenotypes. Thus, these disorders should likely be called *DSPP*-associated dentin defects, with DD type II representing the mild end of the phenotypic spectrum and DI type III representing the severe end.

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Abbreviations used in this paper

DD	dentin dysplasia
DI	dentinogenesis imperfecta
DGP	dentin glycoprotein
DPP	dentin phosphoprotein
DSP	dentin sialoprotein
DSPP	dentin sialophosphoprotein
EDS	Ehlers-Danlos syndrome
OI	osteogenesis imperfecta
SIBLING	small integrin-binding ligand N-linked glycoprotein

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Fig. 1.

Clinical and radiographic features of DI types I–III (**a–g**) and DD types I and II (**h–j**). **a–c** Individuals with DI type I. In this family, affected members also had OI type I due to a missense alteration in *COL1A1* (p.Gly559Cys). **a, b** The constriction of the crown in the cervical region and almost complete obliteration of the pulp chambers. **c** The enamel has fractured from the central and lateral incisors, exposing the underlying yellow-brown dentin. **d, e** An individual with DI type II. **f, g** An affected male from the Brandywine cohort. **h** The extremely short roots characteristic of DD type I. **i** The phenotype in deciduous teeth that resembles DI type II, but the permanent teeth are normal in color. **j** The thistle-tube deformity commonly seen in DD type II.

Fig. 2.

Diagram of the DSPP gene and corresponding protein structure. Mutations are shown above the ge-nomic structure. Gray areas correspond to untranslated regions. The white box corresponds to the signal peptide [amino acids (aa) 1–15]. DSP is shown as black regions (aa 16–382). DGP, represented by a stippled box, corresponds to aa 383–462. The highly repetitive protein, DPP, is shown as a striped box (aa 463–1253).

Table 1

Genes underlying dentin defects

Disorder	Location	Gene
DI type I	17q21.33 7q21.3	<i>COL1A1</i> <i>COL1A2</i>
DI type II	4q22.1	<i>DSPP</i>
DI type III	4q22.1	<i>DSPP</i>
DD type I	unknown	unknown
DD type II	4q22.1	<i>DSPP</i>

Table 2

Mutations in *DSPP* resulting in dentin defects

	Protein	cDNA	Genomic	Diagnosis	References
Exon 2	p.Y6D	c.16T>G	g.16T>G	DI-II	Rajpar et al. [2002]
	p.A15V	c.44C>T	g.44C>T	DI-II	Malmgren et al. [2004]
	p.P17T	c.49C>A	g.49C>A	DI-II	Xiao et al. [2001]
	p.P17S	c.49C>T	g.49C>T	DI-II	this report [2007]
Intron 2	p.V18_Q45del	c.52-3C>G	g.1194C>G	DI-II	Kim et al. [2004]
		c.52-3C>A	g.1194C>A		Holappa et al. [2006]
Exon 3	p.V18F or	c.52G>T	g.1197G>T	DI-II	Xiao et al. [2001]
	p.V18_Q45del			DI-III	Kim et al. [2005]
				DI-III	Song et al. [2006]
				DI-III	Holappa et al. [2006]
	p.Q45X	c.133C>T	g.1278C>T	DI-II	Zhang et al. [2001] Song et al. [2006]
Intron 3	p.V18_Q45del	c.135+1G>A	g.1281G>A	DI-II	Xiao et al. [2001]
Exon 4	p.R68W ^a	c.202A>T	g.1480A>T	DI-II	Malmgren et al. [2004]
Exon 5	Del1160-1171			DI-III	Dong et al. [2005]
	Ins1198-1199 ^a				

All numbering assumes the A of the ATG start codon as nucleotide 1. The reference is NM_014208.

^aThis alteration has been shown to be a normal variant and is not disease causing.