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# Dentinogenesis imperfecta: The Genetic Causes and Outcomes

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## Cover Page Footnote

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# Dentinogenesis imperfecta: The Genetic Causes and Outcomes

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**ABSTRACT**

Dentinogenesis imperfecta (DI) is a genetic disorder characterized by dentin discoloration, tooth development irregularities, and decreased tooth strength. This autosomal dominant disorder is identified in individuals of all ages. There are three classifications of dentinogenesis imperfecta, each with varying presentations and causes. This report covers normal tooth development (odontogenesis), DI development, DI classifications, and the genes involved in this genetic disorder.

## INTRODUCTION

Dentinogenesis imperfecta (DI) is an autosomal dominant developmental disorder that is caused primarily by a mutation in the dentin sialophosphorprotein, or DSPP, gene (Yamakoshi, 2008). COL1A1 and COL1A2 genes are also associated with the disease. Capedepont's teeth and hereditary opalescent dentin are other names that are seen throughout the literature to describe this condition. This hereditary disease leads to incorrect development of both the primary and permanent teeth due to localized mesodermal disruptions. Signs of DI appear as soon as deciduous teeth erupt and complications associated continue throughout one's lifetime (Pai et al., 2012). There are a variety of outcomes that are seen from the DSPP gene mutation. Disruptions in odontogenesis, decreasing tooth strength, and discoloration of the dentition are several of the major consequences of this mutation (Biria et al., 2012).

DI was first identified in 1882 by Barret. It was originally classified as an enamel defect disorder by Witkop, who published the first report of the disease (Witkop et al., 1966). DI was not used until 1939 when Roberts and Schour introduced the term (Jindal et al., 2009; Pai et al., 2012). The current classification system was not introduced until Shields, Bixler, and El-Kafraway identified the three types of DI in 1973 (Pai et al., 2012). The classifications are: DI type I, DI type II, and DI type III (Lee et al., 2013). All three classifications are characterized by hypo-mineralization of dentin and modified dentin structure (Kozma et al., 2018). DI affects approximately 1 in every 6,000 to 8,000 people, according to Beattie, and most individuals will lose permanent dentition (Beattie et al., 2006). Men are more likely to show signs of DI type III than women, although the cause has not yet been identified (Frei et al., 1999). There are several other conditions that present as DI. These include radicular dentin dysplasia, coronal dentin dysplasia, and osteogenesis imperfecta (Wieczorek et al., 2013). This paper will first walk readers through what is typically observed during tooth development and continue by discussing the various proteins and classifications involved with DI and how they affect development. DI impacts roughly less that 2% of the population this paper is written to in an effort to inform and educate, while also supporting the continuation of further research.

## TOOTH DEVELOPMENT

Tooth development, or odontogenesis, begins in utero and is influenced by the mother's diet. There are four main stages in tooth development (Catón and Tucker, 2009). The first stage begins at approximately 6 weeks of pregnancy. The essential materials needed for teeth are formed during this time and a thickening of the dental placode, or dental epithelium, is observed (Catón and Tucker, 2009; Kim et al., 2017). In the first stage, dental epithelium can stimulate odontogenic fate in surrounding neural crest derived mesenchymal tissues to form teeth (Kim et al., 2017). The hard tissues that surround the teeth (enamel, dentin, and cementum) are formed in the next stage at around 3 to 4 months of gestation (Li et al., 2003). Dentin is the tissue that is most affected by all three DI classifications. The outer covering of the tooth, enamel, is a hard-calcified and mineral rich tissue (Goldberg et al., 2011; Li et al., 2003). The enamel tissue cannot repair any damage that occurs, as it does not contain any living cells. Cementum surrounds only the roots of teeth and allows for attachment to the periodontal ligament. The dental pulp is the inner most soft tissue, and it houses the nerves and blood vessels (Li et al., 2003). Dentin is the tissue that follows the enamel and cementum (Goldberg et al., 2011). The final two stages of tooth development occur after birth. The third stage begins when deciduous teeth erupt

from the gums and loss of baby teeth marks the final stage (Catón and Tucker, 2009).

Dentin contains the majority of the mineralized dental tissues. 70% of its make up is mineralized tissues, while the remainder is water and organic matrix. Dentinogenesis is the developmental process of dentin formation. (Goldberg et al., 2011). Dentin is comprised of microscopic tubules. Polarized mammalian odontoblast produce orthodentin, which dentin tubules are characterized by. Tubule size is around 2 to 4 micrometers, and the number of tubules is approximately 18,000 to 21,000 per 2 millimeters. Several different types of dentin have been identified that make up the entire dentine structure. These types include mantle dentin, intertubular dentin, peritubular dentin, primary dentin, secondary dentin, tertiary dentin, and reparative dentin. Each dentin type differs slightly in its overall makeup. Mantle dentin, the outermost dentin layer, of mammalian teeth is 15 to 30 micrometers thick (Goldberg et al., 2011). The largest layer is circumpulpal dentin. In the early stages of dentinogenesis this layer is thin but thickens approximately 4 millimeters daily. Primary and secondary dentin are two types of circumpulpal dentin. Primary dentin is formed during odontogenesis by odontoblast cells. Secondary dentin begins to form as soon as antagonistic cusps are produced and continues to develop throughout one's lifetime. In the early stages of dentinogenesis, odontoblasts are parallel with the basement membrane that will eventually detach and develop into matrix vesicles that aid in early dentin mineralization. First, pre-odontoblast cells become pre-secretory polarizing odontoblasts during their migration to the para-axial mesenchyme. Eventually these cells will aid in bud formation. Next, odontoblast cells will differentiate and begin carrying out specified functions (Goldberg et al., 2011).

Odontogenesis is the developmental process of the dental tissues, and it also requires several stages. These stages include initiation, bud stage, cap stage, bell stage, and advanced bell stage (Nanci, 2013). Initiation is denoted by differentiation of the vestibular lamina and dental lamina. At approximately 6 to 7 weeks of embryonic development the tooth bud connects to the epithelial layer of the mouth through the assistance of the dental lamina. Each stage is controlled by molecular signals from a signaling center. The bud stage is identified when epithelial cells have no clear arrangement, shape, or function. Epithelial cells begin to migrate into the jaw ectomesenchyme at about 8 weeks of embryonic development (Kim et al., 2017; Nanci, 2013). The tooth bud is group of epithelial cells that divide along the boundary of the dental lamina. Condensation of the ectomesenchyme occurs. This is the process when cellular density begins to increase with the neighboring epithelial outgrowth (Nanci, 2013).

When ectomesenchymal cells stop producing extracellular substances, these cells can aggregate and form the dental papilla. The dental papilla will form the dental pulp and dentin during later stages. This marks the cap stage. This stage is easily identified histologically by a more structured cell arrangement (Nanci, 2013). The tooth bud becomes larger as it begins to grow around the ectomesenchymal cells that have accumulated (Kim et al., 2017; Nanci, 2013). This forms that cap, or enamel organ, that will become the enamel that covers the dental pulp. Histodifferentiation and morphodifferentiation occurs during the bell stage. As the inner surface of the cap deepens the enamel organ becomes bell shaped. The hard tissues of the tooth crown are developed during this stage and reach full size (Nanci, 2013). Epithelial cells that migrated to the periphery of the enamel organ differentiate into 4 different cell layers: outer enamel epithelium, inner enamel epithelium, stellate reticulum, and stratum intermedium. During this stage the dental lamina break down so that the developing teeth are now separated from the oral cavity epithelium. These will rejoin once the teeth erupt from the mouth (Kim et al., 2017). In the final stage, advanced bell stage, hard tissues mature, and other important cellular changes occur. The organic matrix is secreted by odontoblast that is used for dentin formation. Dentin begins forming on the outside surface and progresses inward. The secreted matrix mineralizes and becomes the initial layer of enamel. Blood supply is decreased to the area that will become the pulp and pioneer nerve fibers approach the developing structures (Kim et al., 2017; Nanci, 2013). The tooth germ (tooth organ) is created from the enamel organ, dental papilla, and the dental follicle and is controlled by the primary enamel knot (Kim et al., 2017). The primary enamel knot is a signaling center located at the tip of the tooth bud and when fully developed will express BMP, FGF, Shh, and Wnt signaling families (Thesleff et al., 2001).

## RELEVANT PROTEINS

### *SIBLING Proteins*

The SIBLING (small integrin-binding ligand N-linked glycoprotein) family is a group of phosphoproteins that are secreted and then modified post-translationally (Tagliabracci et al., 2015). Chromosome 4 houses these proteins (Zhang et al., 2010). The SIBILING proteins are a type of non-collagenous proteins (NCPs) found in the extracellular matrix and bone. It is thought that NCPs initiate and modulate the mineralization of collagen fibers found in early dentin and bone structures. More recent studies show that some of these proteins are involved in signaling, pathway activation, and organ development.

NCPs mutations result in phenotypic abnormalities of bone and dentin (Huang et al., 2008). Some of the relevant SIBILING proteins involved are dentin matrix protein (DMP1), bone sialoprotein (BSP), dentin sialophosphorprotein (DSPP), and osteopontin (OPN). There are similarities in these proteins such as the presence of integrin-binding Arg-Gly-Asp tripeptide, function, and post-translational modifications (Zhang et al., 2010). These modifications include phosphorylation, glycosylation, and RGD cell binding sequence (Staines et al., 2012).

DSPP is has similarities to DMP1 and is discussed in further detail later in this paper. DMP1 helps to control bone mineralization (Alam et al., 2014). DMP1 mutations in humans result in hypophosphatemic rickets, a disorder that arises from defects in bone mineralization (Huang et al., 2008). Although the primary role of BSP is unknown, it is seen in bone, mineralizing cartilage, dentin, and cementum. BSP differs from other SIBILNG proteins because is it exclusively found in mineralized tissues. It is believed that it is a nucleator for apatite crystal formation which is needed in early bone and dentin development. OPN can also be referred to as phosphoprotein 1 (SPP1). Large quantities of OPN are expressed in mineralized tissues such as bone, cementum, tertiary dentin, and predentin (Zhang et al., 2010). OPN can also be found in some cells and non-mineralized tissues (Huang et al., 2008). The relationship between DI and the SIBILING family are discussed in the following paragraphs.

### *DSPP Gene*

Dentin sialophosphorprotein (DSPP) is the primary gene involved in DI and results in 2 of the 3 allelic DI types: DI type II and dentinogenesis type III (Yamakoshi, 2008). DSPP is located in salivary glands, kidneys, lungs, and several other tissues and is predominately expressed in odontoblast (Yamakoshi, 2008). Its expression is hundreds of times higher in dentin tissue (Barron et al., 2008). This gene is a chimeric extracellular matrix protein composed of dentin sialoprotein (DSP), dentin glycoprotein (DGP), and dentin phosphoprotein (DPP), that are each cleaved by proteases from the astacin and MMP families (de La Dure-Molla et al., 2015; Yamakoshi, 2008). The DSPP gene is positioned on chromosome 4q21, which encodes key noncollagenous proteins of the dentin matrix and is secreted extracellularly (Fisher et al., 2012; Lee et al., 2013). The consequence of mutations is defective dentin mineralization (Lee et al., 2013).

Collagen fibers make up the framework for mineralization because of its tensile strength to allow for dentin flexibility (Yamakoshi, 2008). DSPP derived noncollagenous proteins are produced by proteolysis of DSPP. These proteins have hundreds of post-translational modifications that occur. DPP binds to calcium build up and enables early mineralization (Fisher et al., 2012). DPP is an acidic protein and its length differs among species (Lee et al., 2013; Yamakoshi, 2008). It is disordered, highly phosphorylated, and has many polymorphisms because of its heterogeneous coding region (Yamakoshi, 2008). DPP will initiate hydroxyapatite formation in vitro at low concentration and inhibit growth at higher concentrations. This will control mineralization in different areas and under specific conditions (de La Dure-Molla et al., 2015). DSP is the N-terminus domain of the DSPP gene, while DGP is the middle section. DSP is a sialic acid-rich proteoglycan that forms covalent dimers (Yamakoshi, 2008). It will undergo only a few phosphorylations that aid in differentiation and growth of the dental pulp through signaling pathways like BMP and MAPK (de La Dure-Molla et al., 2015; Ritchie, 2016). DGP is an 81 amino acid segment and has 4 phosphorylated serine residues and one glycosylated asparagine. DSP and DPP appear to have more involved roles than DGP during dentinogenesis but this is not yet understood (Park et al., 2020).

### *COL1A1 & COL1A2*

COL1A1 and COL1A2 genes are involved in DI type I. COL1A1 is found on chromosome 17 and COL1A2 is located on chromosome 7 (Church et al., 1981). Mutations result in mineral disproportion, a decrease in dentin strength, dentin discoloration, and sparse tubules (Nutchoey et al., 2021). Collagen type I is important during dentinogenesis as it is a main element of pre-dentin that is formed during development (Kantaputra et al., 2018). These genes encode the α-1 and α-2 polypeptide chains that are the scaffolding of type I collagen (Ibrahim et al., 2019). COL1A1 and COL1A2 code for a majority of the collagenous make up found in the dentin matrix (Park et al., 2020).

Any mutations lead to irregular collagen fibers. Glycine is found in the center of the protein and substitutions are the most common mutations that occur. This mutation involves a glycine substitution at the carboxyl terminus (Nutchoey et al., 2021). One role of glycine is to stabilize collagen triple helices, any disruption leads to DI type I and osteogenesis imperfecta. Mutations have also been found to cause developmental problems in bone structure as well (Ibrahim et al., 2019). COL1A2 mutations are rare but can still lead to DI. They also most commonly involve substitutions (Ibrahim et al., 2019; Pope et al., 1985).

Osteogenesis imperfecta and Ehlers-Danlos syndrome, cardiac valvular type (EDSCV) result from COL1A1 and COL1A2 mutations as well. Ehlers-Danlos syndrome involves several connective tissue disorders that lead to articular hypermobility and tissue fragility. It is an

autosomal recessive disorder. Individuals with EDSCV have mitral valve prolapse, aortic insufficiency, and mitral regurgitation along with other complications of this syndrome (Nuytinck et al., 2000). Osteogenesis imperfecta (OI) , or brittle bone disease, is a connective tissue ailment that results in frequent bone fractures and various skeletal deformities (Biria et al., 2012). There are 4 main types that have been classified: OI type I, OI type II, OI type III, and OI type IV.

## DENTINOGENESIS IMPERFECTA TYPE I

People with DI type I will also develop osteogenesis imperfecta (OI), commonly called brittle bone disease (Barron et al., 2008). Individuals with DI type I will always have OI, sometimes referred to as OIDI (Muñoz et al., 2016). In a study carried out by researchers at Shahed University, in Iran, it was found that 50% of individuals with osteogenesis imperfecta have DI type I. While both dentitions are affected, primary teeth are more aggressively affected by DI type I (Biria et al., 2012). COL1A1 and COL1A2 glycine substitutions are often responsible for type I collagen malformation that cause these diseases (Ibrahim et al., 2019). These genes encode the pro-alpha1 and pro-alpha 2 polypeptide chains found in this collagen type (Abukabbos and Al-Sineedi, 2013). Approximately 85% of organic material found in dentin is collagen type I. Typically collagen will be arranged in consistent interrupted striations, but OIDI disrupts this organization and causes vulnerability to fractures. Dental collagen does not renew like its counterpart found in bone, making any maldevelopment significantly affect tooth integrity (Ibrahim et al., 2019).

Persons with DI type I are typically shorter than average due to the association with brittle bone disease (Biria et al., 2012; Nuytinck et al., 2000). Dentition is weak, and coloring is described as amber and translucent (Barron et al., 2008). Tooth roots develop shorter than average and commonly lead to damage of the dental pulp. Development of a bulbous tooth crown interferes with the cement-enamel junction, affecting dental pulp as well (Ibrahim et al., 2019). Circumpulpal dentin is the most affected dentin layer seen in this condition (Biria et al., 2012). OIDI individuals may also have hearing loss, blue sclera, asthma, and spinal curvature (Abukabbos and Al-Sineedi, 2013). Blue sclera is another consequence of the COL1A1 and COL1A2 mutations that OIDI individuals have. Collagen type I is important in several tissues found in the eye, such as uveal tissues and cornea layers. Cornea thickness is affected leading to ocular conditions like myopia and astigmatism (Hald et al., 2018). Dental development is connected to craniofacial development, originating from pluripotent neural crest cells that move into the first pharyngeal arch (Kozma et al., 2018). Craniofacial organogenesis is affected by COL1A1/ COL1A2 mutations and can lead to a rounded face shape and hearing loss (Hald et al., 2018; Kozma et al., 2018). Hearing loss occurs due to developmental irregularities of the labyrinth and temporal bone. Fractures of the inner ear ossicles have been observed to affect hearing (Hald et al., 2018).

## DENTINOGENESIS IMPERFECTA TYPE II

In DI type II, the dentin sialophosphorprotein (DSPP) gene needed for regular tooth development is affected so there are no other disorders inherited as seen with DI type I (Beattie et al., 2006). Mutated DSPP produces odontoblasts that cannot develop into fully working cells that secrete collagen for normal tooth development. This causes hypo-mineralization that will not develop structurally sound dentin tubules (Pai et al., 2012). DI type II is radiologically, clinically, and histologically alike to dentinogenesis type I except it is not inherited with osteogenesis imperfecta (Kozma et al., 2018).

DI type II is considered as the most moderate form of the disease and is observed in approximately 1 in every 8,000 births (de La Dure-Molla et al., 2015). Teeth are characterized by grey-blue or amber and opalescent coloration (de La Dure-Molla et al., 2015). It is seen that the enamel is broken down during mastication, quickly exposing the dentin layer (Fisher et al., 2012). This phenomenon will cause irregular organization of the dental-enamel junction. Eventually, separation of the enamel and dentin can be observed, some researchers believe this is due to reduced blood supply because the dental pulp is damaged. Hypo-mineralized dentin becomes exposed and oftentimes is eroded so that there is full disappearance of the crown. Periodontal disease is common because of increased permeability of the enamel (Fisher et al., 2012).

The autosomal dominant disorder affects both primary and permanent dentition, although primary teeth tend to have greater damage (de La Dure-Molla et al., 2015). Unlike DI type I all teeth are affected (Barron et al., 2008). Some studies have observed lower amounts of magnesium and higher amounts of sodium in DI type II affected teeth than in normally developed dentition (Park et al., 2020). Severe attrition of the dentin leads to shorter teeth and damaged dental pulp. Although the enamel is not affected by this gene defect, it is susceptible to more frequent fracturing because the dentin structure underneath in not well developed (Zhang et al., 2001). Hearing loss is rare but has been reported in older individuals with DI type II (Barron et al., 2008). Incorrect dentin formation will also generate extremely large pulp chambers, as well as short and thin roots (Fisher et al., 2012). Mutations that occur at the 3’ end of DSPP lead to DI type II (Fisher et al., 2012). After secretion, DSPP is

cleaved into DSP, DGP, and DPP proteins by proteases early in tooth development (Yamakoshi, 2008).

DMP1, BSP, and SPP1 genes have been mapped to the 4q21 chromosome and can potentially lead to DI type II (Zhang et al., 2001). These genes are also involved in normal tooth development (Dean et al., 1997). Dentin matrix acidic phosphoprotein contains 5 exons. DMP1 is a dentin specific protein that is serine rich and has multiple sites of phosphorylation. It is closely linked to DI type II but individuals with a mutation of this gene will more commonly develop rickets, osteomalacia, and normocalciuria. BSP goes through many posttranslational modifications and is involved in around 12% of the noncollagenous proteins made. It is synthesized by skeletal associated cells, such as osteoblasts and chondrocytes. BSP includes 6 introns and 1 large exon. Similarly, to DMP1, this gene is linked to DI but individuals typically will express diseases like Fibrous Dysplasia and Chondromalacia. According to Dean, secreted phosphoprotein 1 (SPP1) belongs to the SIBLING family (Dean et al., 1997). It is also referred to as Osteopontin, or OPN, and is expressed in dentin tissue. SPP1 mRNA can be found as early as 8 weeks of gestation in the placenta. SPP1 is made by osteoblasts when stimulation by calcitriol occurs, causing it to bind to hydroxyapatite. This allows for proper anchoring of osteoclast cells to the bone matrix mineral material. SPP1 is involved in mineralized tissue growth and crystal nucleation modulation in order to control conditions that involve mineral precipitation (Foster et al., 2018). BSP and SPP1 are linked closely and have many similarities. BSP does not have a range as large as SPP1. SPP1 has been identified in elastic tissues of the heart and is produced in tissues of the ear and kidney. A variety of skin diseases are more likely to be seen in someone with an osteopontin mutation, as it is extremely rare to develop DI type II (Dean et al., 1997).

## DENTINOGENESIS IMPERFECTA TYPE III

DI type III is also classified as Brandywine type DI (Witkop et al., 1966). It is the rarest and most severe form of the disease. It is found in a small inbred population located in southern Maryland, seeing 1 in 15 individuals in this area with the disorder (Ibrahim et al., 2019). This population is known as the Brandywine isolate (Frei et al., 1999). Dentin is smooth and amber/yellow or blue/grey in color. Similarly to DI type II, osteogenesis imperfecta does not occur (Schimmelpfenning and McDonald, 1953). Teeth of individuals with DI type III have very little dentin, shell teeth that appear hollow, and exposed pulp (Barron et al., 2008; Pai et al., 2012). Permanent teeth are rapidly damaged causing the pulpal space to become significantly smaller or disappear completely.

While it is aslo caused by DSPP mutations, Brandywine type dentogenisis imperfecta differs from DI type II. A frameshift mutation that occurs at the 3’ end of DSPP leads to DI type III. Brandywine type DI has enlarged pulp chambers in early tooth development and enamel pitting, this is not commonly seen in DI type II (Witkop et al., 1966). Multiple periapical radiolucency bone loss is seen in DI type III teeth (Fisher et al., 2012). DI types II and III are considered to be phenotypic variations of the same disease, not two separate conditions. These two classifications are allelic types of DI (Shields et al., 1973). Researchers at Seoul University School of Denistry discovered a mutation on the second exon at the second nucleotide position of DSPP that leads to Brandywise type DI. Pre-mRNA splicing was not altered despite the close distance to the exon-intron boundary (Lee et al., 2013). This resulted in a missense mutation that switched a highly conserved proline to a leucine. This change can affect signal peptide cleavage depending on its location to the cleavage site. While both proline and leucine are nonpolar, neutral amino acids, their hydropathy indexs differ causing decreased signal peptide probability. DSP, dentin sialoprotein, expression and secretion are decreased significantly in DSPP gene mutants. Transport of DSP was also affected. Normally DSP will be transported to the Golgi apparatus, but mutants were kept in the endoplasmic reticulum (Lee et al., 2013).

## TREATMENT

There have not been any treatments identified to combat problems that occur for individuals with DI. Procedures that are carried out serve functional and aesthetic purpose, but the condition will still progress. It is recommended that any treatment is performed early on primary teeth in order to help correctly develop the face. Genetic counseling is also recommended for individuals with all DI types (Barron et al., 2008).

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