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RESEARCH LETTER

Isolated dentinogenesis imperfecta with glass-like enamel caused by *COL1A2* mutation

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TO THE EDITOR:

Isolated dentinogenesis imperfecta or hereditary opalescent dentin or dentinogenesis imperfecta, type II (DGI1: MIM #125490) is an autosomal dominant genetic disorder, characterized by severe hypomineralization of dentin with abnormal dentin structure affecting both primary and permanent dentitions. Clinically all teeth appear blue gray or amber brown, and opalescent. Primary teeth are more severely affected than the permanent ones (de La Dure-Molla, Philippe Fournier, & Berdal, 2015; Kim & Simmer, 2007).

We report clinical and molecular findings of a Thai family affected with DGI1. The proband (II-5) and six affected family members had glass-like appearance of the enamel of the primary incisors (Figure 1a, b). All affected members had a heterozygous missense mutation in *COL1A2*. The enamel with glass-like appearance found in our patients shows that not only dentin and cementum (Kantaputra et al., 2018) but also enamel is abnormal in teeth affected with DGI, and suggests a potential structural role of collagen type I in enamel biomineralization. All family members had DGI1 in both primary and permanent dentitions. Interestingly, some of them had DGI1 teeth and normal permanent teeth in the same persons.

Oral examination of the proband (patient II-5) was performed 25 years ago when he was one and a half years old. Four primary incisors were erupted and the enamel was remarkably translucent and had glass-like appearance (Figure 1a). Dental X-rays were not taken. He has been healthy with no history of bone fracture. It was reported that the enamel of the primary incisors of the proband (II-5) was more translucent than that of other affected family members (Figure 1a). At

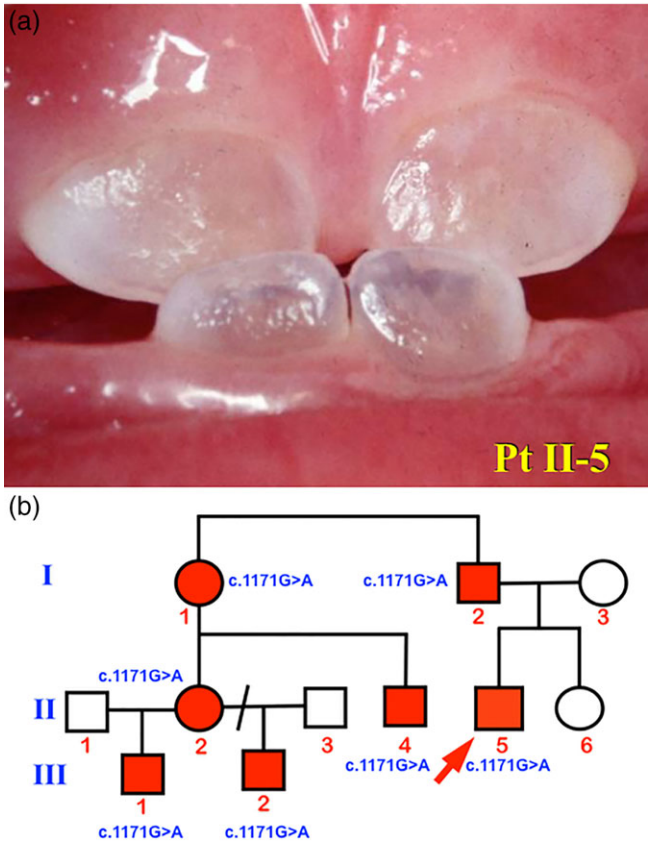

FIGURE 1 (a) Primary incisors of the proband (II-5). Glass appearing enamel. Teeth are remarkably translucent. (b) Pedigree showing autosomal dominant mode of inheritance with complete penetrance [Color figure can be viewed at wileyonlinelibrary.com]

FIGURE 2 (a) Patient I-1. (b) Patient II-2. (c) Patient III-1. (d) Patient III-2. (e, f) Teeth of Patient 1-I. (g, h) Teeth of Patient II-2. All permanent teeth of patients I-1 and II-2 are yellow, brown, and black discoloration with severe dental attrition and enamel dislodgement of their permanent teeth. Teeth of patient I-1 are more discolored than that of patient II-2 [Color figure can be viewed at wileyonlinelibrary.com]

age 26 years he was not available for clinical examination. Clinical examination of patients I-1, II-2, III-1, and III-2 at ages 44, 27, 9, and 7 years, respectively, revealed normal facial features and hearing without blue sclerae (Figure 2a–d). The heights with means and standard deviations or centiles of the family members are as followed I-2 (150 cm; 166.3 ± 6.0 cm), I-3 (155 cm; 156.4 ± 5.3 cm), II-5 (168 cm; 166.5 ± 6.2 cm), II-6 (153 cm; 159 ± 5.9 cm), II-2 (161 cm;159 ± 5.9 cm), III-1 (126 cm; 125 ± 5.5 cm), and III-2 (108 cm; 108.7 ± 4.4 cm).

Oral examination of patients I-1 and II-2 revealed yellow, brown, and black discoloration with severe dental attrition and enamel dislodgement of their permanent teeth. Interestingly, the maxillary permanent central and lateral incisors of patient II-2 appeared normal (Figure 2e–h). Teeth of patients III-1 and III-2 were in mixed dentition (Figure 3a,b). Teeth of patient III-1 had yellow and brown discoloration except for the maxillary permanent central and lateral incisors which appeared normal (Figure 3a). Teeth of patient III-2 had yellow and brown discoloration except for the mandibular permanent central incisors, which appeared normal (Figure 3b). Severe dental attrition and enamel dislodgement of the primary teeth of patients III-1 and III-2 was evident (Figure 3a,b).

Panoramic radiographs of patients I-1, II-2 showed bulbous crowns, dental pulp obliteration, and periapical radiolucent areas as a result of dental infections (Figure 4a,b). Mandible of patients I-1 and II-2 appeared denser than normal. The mandibular condyles of patient I-1 were less dense than usual. Panoramic radiographs of patients III-1 and III-2 showed mixed dentitions and bulbous crowns. The dentin of the developing permanent teeth was less radiopaque than normal. The dental pulps of the developing permanent teeth appeared large as a result of abnormal mineralization of dentin (Figure 5a,b). Lateral cephalographs of patients I-1, II-2, III-1, and III-2 were unremarkable without signs of osteopenia (Supporting Information Figure S1).

Whole exome sequencing of six affected and three unaffected family members showed a heterozygous base substitution c.1171G > A (NM_000089.3; rs67707918) in exon 21 of *COL1A2* (Supporting Information Figure S2). This heterozygous base substitution co-segregate with the DGI phenotype in the family in autosomal dominant mode of inheritance with complete penetrance (Figure 1b). The variant was also predicted using in silico functional annotation software to be amino acid substitution p.Gly391Ser (Ggc/Agc; NP_000080.2). The altered residue Gly391 is conserved across all species (Supporting Information Figure S3).

In the collagen triple helix structure, the Gly-Xaa-Xaa repeat is necessary to allow formation of the triple helix, since the only amino acid that can fit in that position is Gly, which is highly conserved. As shown in Figure 6, mutation of this position (at Gly391) to Ser, points

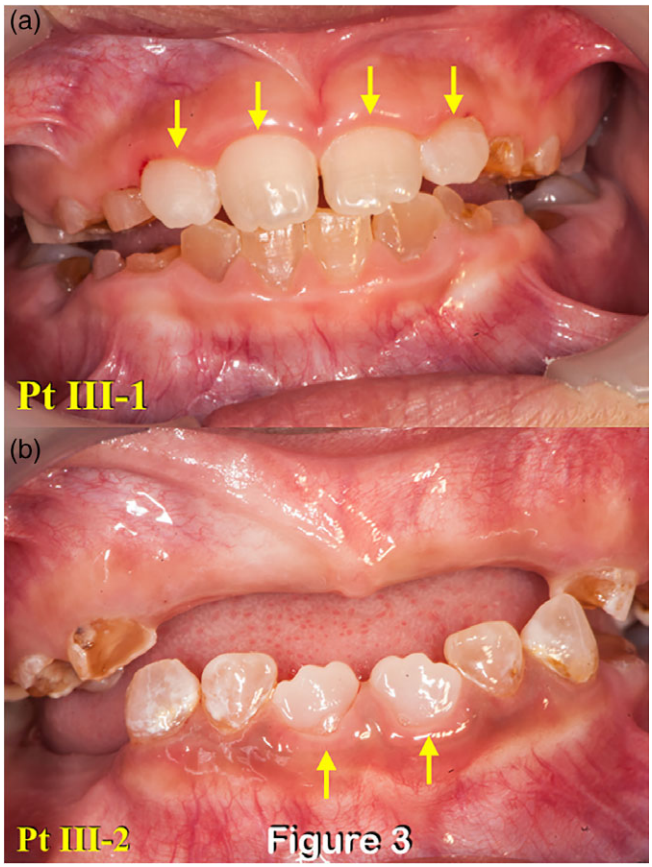

FIGURE 3 (a) Teeth of patient III-1. Mixed dentition. All teeth are discolored, except for the maxillary permanent central and lateral incisors which appear normal (arrows). Severe dental attrition and enamel dislodgement are noted. (b) Teeth of patient III-2. All teeth are discolored, except for the mandibular permanent central incisors, which appear normal (arrows). Note severe dental attrition and enamel dislodgement [Color figure can be viewed at wileyonlinelibrary.com]

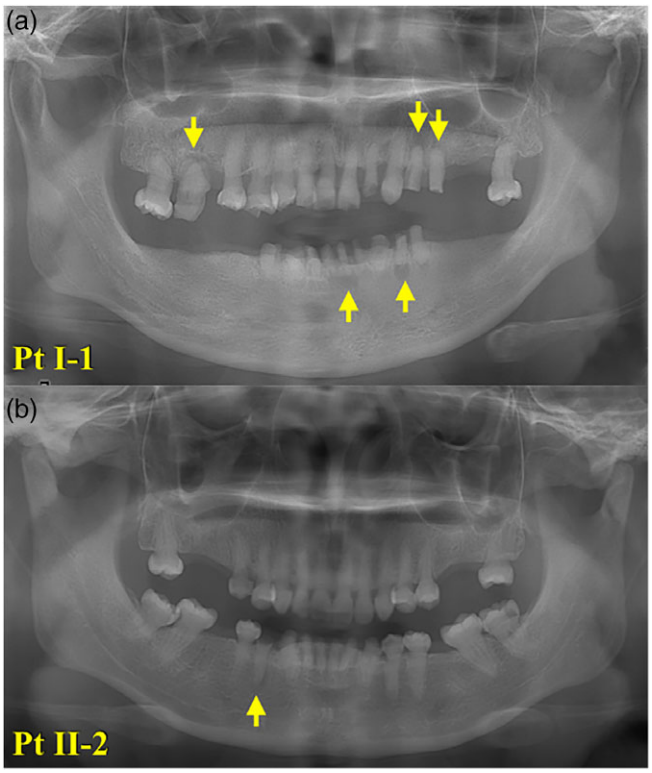

FIGURE 4 Panoramic radiographs of (a) Patient I-1. (b) Patient II-2. Bulbous crowns of permanent molars. Dental pulp obliteration. Periapical radiolucent areas as a result of dental infections (arrows). Note dense mandibles of patients I-1 and II-2. The mandibular condyles of patient I-1 are less dense than usual [Color figure can be viewed at wileyonlinelibrary.com]

the side chain toward the other two chains, where it will make steric contacts and push the other two chains away, as indicated by the red arrows in the picture. This will disrupt the triple helix structure and collagen structural function (Figure 6). In support of this assessment, Mutation Taster, PolyPhen-2, and SIFT predicted this variant as "disease causing" (0.9999), "probably damaging" (1.000), and damaging (0), respectively. Furthermore, this variant was not found in 200 exome data of our non-OI controls or in the ExAC and gnomAD databases.

The p.Gly391Ser mutation in *COL1A2* has been reported in a sporadic patient affected with DGI and hypodontia (Wang, Chan, Makovey, Simmer, & Hu, 2012). Hypodontia was reported to be caused by a mutation in *PAX9*. However, glass-like appearance of the enamel was not reported. The same mutation has also been reported in patient affected with OI type III, however, dentin defects were not mentioned (Marini et al., 2007). This suggests phenotypic variability in cases with the same *COL1A2* mutation, which may be the result of different genetic backgrounds of the patients. Except for patient I-2 who was somewhat short, the heights of the affected and the unaffected family members range from average to somewhat short. Absence of brittle bones and hyperflexible joints in all family members rules out osteogenesis imperfecta. However, we do not know if dense mandibles of patients I-1 and II-2 were the consequences of *COL1A2* mutation or coincidences.

The grandmother (I-1), the mother (II-2), and two sons (III-1 and III-2) had different severity of DGI1. The degrees of tooth discoloration in this family appeared to positively relate to the severity of DGI1 and negatively relate to the strength of teeth. That was why teeth with darker discoloration had more severe dental attrition. Patient II-2 was affected with DGI1, but her maxillary permanent central and lateral incisors were unremarkable. Having both normal appearing permanent incisors and DGI1 teeth in patients II-2, III-1, and III-2 is unique, because DGI1 generally affects both dentitions, although with greater severity in the primary dentition. Having DGI1 teeth and normal teeth in the same persons has never been reported. Andersson et al. (2017) reported patients who had DGI in primary dentition but not in the permanent dentition. The majority of the OI patients (80%) with missense mutation in *COL1A2* with DGI only in their primary and not in permanent dentition had missense mutations located C-terminal of pGly469, while those with DGI in both dentitions had substitutions for a glycine located between p.Gly286 and p.Gly391 (Andersson et al., 2017). Our patients carried p.Gly391Ser mutation and had DGI in both dentitions but some of the permanent teeth were not affected with DGI. Thus, besides intrafamilial variability, the family members we report here also showed phenotypic variability even within the same persons.

Since *COL1A2* mutations usually lead to OI, Dual-energy X-ray absorptiometry (DEXA) was performed in the available patients (I-1

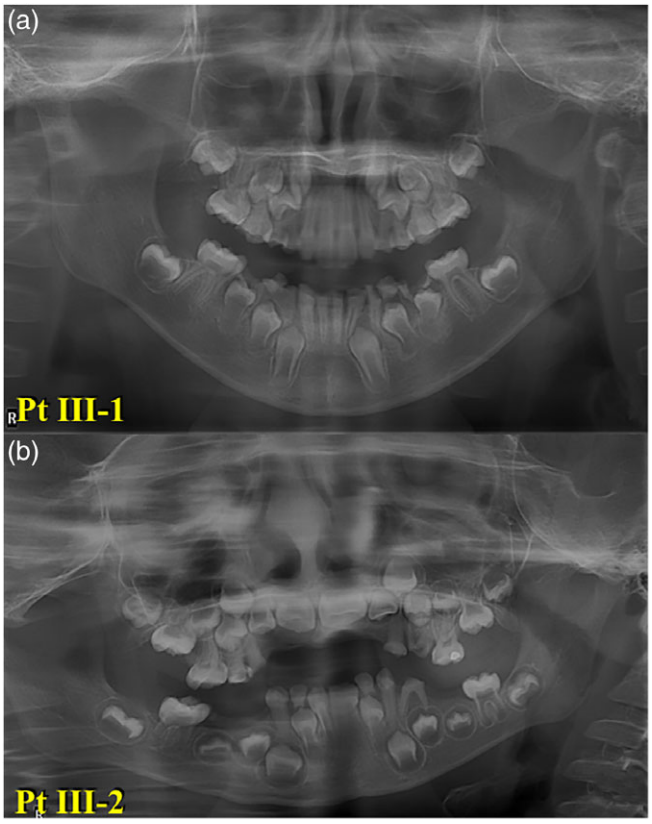

FIGURE 5 Panoramic radiographs of (a) Patient III-1. (b) Patient III-2. Teeth are in mixed dentitions. The dentin of the developing permanent teeth is less radiopaque than normal. The dental pulp chambers and root canals of the developing permanent teeth are larger than normal. Note dense mandibular bones [Color figure can be viewed at wileyonlinelibrary.com]

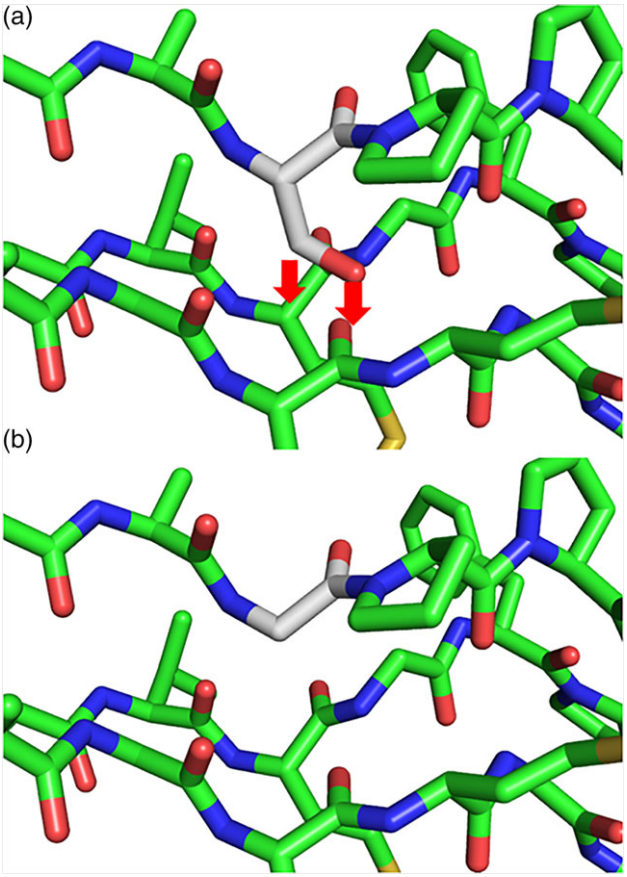

FIGURE 6 Effect of the Gly391Ser mutation on the collagen triple helix structure. (a) Mutant protein model. The Gly391 position is mutated to Ser391, shown with gray carbons. Since this sidechain points directly between the other two strands of the triple helix, it will push those strands away, as indicated by the red arrows, and thereby disrupt the structure and function. (b) Wild type protein model. No such clash is seen in the wild type helix, in which the strands are well-separated in this position [Color figure can be viewed at wileyonlinelibrary.com]

and II-2) in order to evaluate if they had ostepenia. It was not performed in patients III-1 and III-2 because there are no bone mineral density norms for children. Dual-energy X-ray absorptiometry of the 44-year-old female patient (I-1) performed at the lumbar spine L1–L4 showed BMD of 0.980 g/cm^2 (*T*-score = −1.1; *Z*-score = −1.2). Bone mineral density at left femoral neck was 0.637 g/cm^2 (*T*-score = −2.3; *Z*-score = −1.9). The BMD at L1–L4 of II-2, who was 27 years old female, was 1.115 g/cm^2 (*T*-score = 0.0; *Z*-score = −0.3). Her BMD at the left femoral neck was 0.877 g/cm^2 (*T*-score = −0.6; *Z*-score = −0.8). It is concluded that the BMD of both patients are in the expected ranges for their ages.

Dentinogenesis process consists of secretion of extracellular matrix (predentin) by odontoblasts, followed by mineralization of predentin. Collagen type I is the major component of predentin (90%) and the remaining 10% is non-collagenous proteins and lipids. Dentinogenesis imperfecta, type II, a disorder of extracellular matrix of dentin, has been reported to be caused by mutations in *DSPP* (de La Dure-Molla et al., 2015). *DSPP* encodes for a single mRNA giving three proteins including DSP (dentin sialoprotein), dentin glycoprotein (DGP), and dentin phosphoprotein (DPP). Dentinogenesis imperfecta can be associated with a number of genetic disorders especially OI, a group of brittle bone disorders caused mainly by mutations in *COL1A1*, and *COL1A2* (Kantaputra, 2001; Kantaputra et al., 2018). It is noteworthy that the clinical and radiographic features of DGI caused by mutations in *DSPP*, *COL1A1*, and *COL1A2* are not distinguishable. This may be because in normal situation DPP binds to collagen fibrils during hydroxyapatite nucleation (Huq et al., 2005). It is noteworthy that unlike DGI caused by mutations in *COL1A1* and *COL1A2*, having DGI1 teeth in primary but not permanent teeth has not been reported in DSPP-associated DGI1 (Andersson et al., 2017; Kim & Simmer, 2007) and having DGI and normal teeth in the same persons has not been reported to be associated with mutations in *DSPP*, *COL1A2*, or *COL1A1*.

Here, we report the first family affected with DGI1 caused by a mutation in *COL1A2*. The glass-like enamel appearance and the presence of both normal permanent teeth and DGI teeth in the same persons are unique. The glass-like appearance of enamel reflects the structural role of collagen type I in mineralization of enamel. Phenotypic variability within the same persons implies that all permanent teeth are not equally affected by this *COL1A2* mutation. This report demonstrates that a mutation in *COL1A2* can cause DGI1 and shows that not only dentin and cementum but also enamel is abnormal in teeth affected with DGI. Phenotypic variability found in patients raises important notions. The same mutation found in our family with DGI1 caused OI type III in another patient (Marini et al., 2007). If we

find out what factor gives our patients the OI-free phenotype, we may be able to use it as a therapeutic approach to treat patients with OI.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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