Dental and facial characteristics of osteogenesis imperfecta type V

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19 **Abstract**

20 Osteogenesis imperfecta (OI) type V is an ultrarare heritable bone disorder caused by the heterozygous
 21 c.-14C>T mutation in *IFITM5*. The dental and craniofacial phenotype has not been described in detail.
 22 In the present multicenter study (Brittle Bone Disease Consortium) 14 individuals with OI type V (age 3
 23 to 50 years; 10 females, 4 males) underwent dental and craniofacial assessment. None of the individuals
 24 had dentinogenesis imperfecta. Six of the 9 study participants (66%) for whom panoramic radiographs
 25 were obtained had at least one missing tooth (range 1 to 9). Class II molar occlusion was present in 8
 26 (57%) of the 14 study participants. The facial profile was retrusive and lower face height was decreased
 27 in 8 (57%) individuals. Cephalometry, performed in three study participants, revealed a severely
 28 retrusive maxilla and mandible, and poorly angulated incisors in a 14-year old girl, a protrusive maxilla
 29 and a retrusive mandible in a 14-year old boy. Cone beam computed tomography scans were obtained
 30 from two study participants and demonstrated intervertebral disc calcification at the C2-C3 level in one
 31 individual. Our study observed that OI type V is associated with missing permanent teeth, especially
 32 permanent premolar, but not with dentinogenesis imperfecta. The pattern of craniofacial abnormalities in
 33 OI type V thus differs from that in other severe OI types, such as OI type III and IV, and could be
 34 described as a bimaxillary retrusive malocclusion with reduced lower face height and multiple missing
 35 teeth.

36

37 **Keywords:** Osteogenesis Imperfecta, Craniofacial, Oligodontia, Dental, Fractures; *IFITM5*

38

39 **Introduction**

40 Osteogenesis imperfecta (OI) is a heritable connective tissue disorder that is associated with bone
41 fragility and often short stature (1). About 90% of individuals with a clinical diagnosis of OI have
42 variants in *COL1A1* and *COL1A2*, the genes encoding collagen type I alpha chains (2). Clinically, such
43 patients are classified into OI types I (least severe form), OI type II (perinatal lethal), OI type III
44 (severe), OI type IV (moderate severity). There is presently no cure for OI, but bisphosphonate drugs are
45 widely administered to increase bone density and decrease the number of fractures (1). Apart from
46 fractures in long bones and vertebra, individuals with *COL1A1*- and *COL1A2*-related OI often have
47 dental and craniofacial abnormalities, including dentinogenesis imperfecta (DI), tooth agenesis and
48 malocclusion (3-5).

49 Among OI types not caused by *COL1A1* or *COL1A2*, OI type V is the most prevalent disorder (6). OI
50 type V is caused by the recurrent heterozygous c.-14C>T variant in *IFITM5*, which encodes BRIL, a
51 transmembrane protein with unknown function that is specifically expressed in osteoblasts (7-9). The
52 variant creates a new translational start site and leads to the addition of 5 amino acids at the N-terminus
53 of the BRIL protein. OI type V resembles OI type IV with regard to fracture incidence, long-bone
54 deformities, vertebral compression fractures and scoliosis (10, 11), but also has distinguishing features
55 such as hyperplastic callus formation and calcification of the interosseous forearm membrane (10, 12).
56 How the addition of 5 amino acids to BRIL protein leads to bone fragility is unknown at present. Mouse
57 models harboring the OI type V variant die at birth, which complicates mechanistic studies (13, 14).

58 Although OI type V seems to lead to similar bone material abnormalities and bone fragility as OI type
59 IV caused by *COL1A1*/*COL1A2* mutations (10, 15), little is known about the involvement of the
60 craniofacial skeleton and teeth in OI type V. Previous reports on OI type V stated that affected
61 individuals did not have clinical signs of DI (10, 16, 17), but missing teeth, short roots and ectopic

eruption of the molars have been reported (17). A prospective, detailed characterization of the craniofacial and dental phenotype in a cohort of OI type V has not been performed.

In the present report we therefore evaluated the dental and craniofacial characteristics in a cohort of individuals with OI type V who were identified through the Brittle Bone Disease Consortium, a multicenter Rare Disease Clinical Research Network.

Materials and Methods

Study Participants

Individuals with a diagnosis of OI type V were recruited through the Brittle Bone Disease Consortium (<https://www.rarediseasesnetwork.org/cms/BBD>) that comprises several specialized centers from across North America (Houston, Montreal, Chicago, Baltimore, Portland, Washington DC, New York, Omaha, Los Angeles). One of the projects conducted by the consortium is a natural history study to assess the clinical features of OI. Patients with a diagnosis of OI of any type and any age are eligible to participate. Dental evaluation is offered to participants who are three years of age or older.

The present study analyzes baseline dental data from the 14 study participants (10 females, 4 males; age range 3 to 50 years) who had a diagnosis of OI type V. Two individuals in addition agreed to participate in an ancillary study involving cone beam computed tomography (CBCT). For 11 individuals, the diagnosis of OI type V was confirmed by genetic testing (heterozygosity for the c.-14C>T variant in *IFITM5*); in 3 participants the diagnosis was based on clinical findings alone. Three cephalometric radiographs were also studied. The study was approved at all participating study centers, and all study participants or their legal guardians provided informed consent.

Craniofacial and dental evaluations

The dental evaluation comprised clinical examination and extra- and intraoral photographs for all study participants, panoramic radiographs for those participants aged six years and older who consented to the test. The study dentist at each site performed the intraoral clinical examination and was responsible for obtaining a standard set of intraoral and extraoral photographs as well as panoramic radiographs. Examiners had been calibrated by passing the simplified International Caries Detection and Assessment System (ICDAS) examination (18). The photographs and radiographs were uploaded to the study website and were independently assessed by two experienced central readers, an orthodontist and an oral radiologist. There were no inter-observer disagreements on the assessments presented here. CBCT scans were evaluated by an oral and maxillofacial radiologist.

The clinical dental examination included assessing the classification of occlusion, overbite, overjet, crowding, open bite, crossbite, arch shape and the presence of DI (said to be present if at least one tooth appearing opalescent or had gray, brown or yellow color). The presence of DI was also assessed by examining panoramic radiographs (radiographic criteria for DI were: partial or complete pulp obliteration, bulbous crown, cervical constrictions, roots abnormalities or short root, and taurodontism). Lateral and frontal photographs were used to assess facial type (normocephalic, brachycephalic or dolichocephalic; facial symmetry; facial proportions), and profile (normal, concave or convex), ear position (19), and frontal bossing. The facial type was determined by using the facial index that was calculated as the ratio between the maximum width to the maximum length of the face on the frontal photograph: dolichocephalic (long and narrow face), <0.72 ; normocephalic, 0.72 to 0.82 ; brachycephalic (short and wide face), >0.82 (20). Facial symmetry was determined by comparing the right and left sides of the face as determined by a reference midline passing through the glabella (midpoint between the eyebrow) and the subnasale points (the junction between the nasal septum and

the upper lip). Facial proportions were calculated as follows: total face height, distance between glabella and soft tissue pogonion (the most anteroinferior point of the chin); upper face height, distance between glabella and subnasale; lower face height, distance between subnasale and the soft tissue pogonion. A lower face height less than 47% of total face height was classified as reduced; a lower face height more than 63% of total face height was classified as increased (21). Profile assessment was performed by measuring the angle between glabella, subnasale, and soft tissue pogonion in a full profile picture. An angle between 158 and 180 degrees was considered normal, regardless of sex (22). An angle <158 degrees indicates a convex profile while an angle >180 degree represents a flat to concave profile.

Lateral cephalometric radiographs were analyzed using the Ceph Tracing routine of the Dolphin Imaging software package (version 11.8). Results were compared to normative cephalometric data as published (23). CBCT scans were acquired with a 3D Accuitomo 170 (Morita Inc, Kyoto, Japan) CBCT machine in a 170 mm x 120 mm field-of-view and a 250 μ m voxel size. The exposure settings for CBCT included a tube voltage of 90 kV and a tube current of 4.5 mA for 17.5 seconds. Image analysis was performed using Anatomage InVivo 5 version 5.4 (Invivo Dental; Anatomage, San Jose, CA) software.

In order to evaluate the projection of the lip and the convexity of the lower face, two measurements were used. The H angle measures the prominence of the lips in relation to the facial line (Nasion soft-tissue pogonion soft: Normal mean value: 6 degrees, standard deviation 3 degrees) (24). The Z angle is used to measure facial balance and measures the prominence of the lips or the relative retrusiveness of the chin. The Z angle is formed by the intersection of the lines Na (soft tissue)-Pogonion (soft tissue) and Pogonion(soft tissue) - most prominent lip point. The normal mean for the Z angle is 10 degrees with a standard deviation of 4 degrees (25).

129 Taking into account frequent reports of hypodontia in patients with OI, to evaluate the caries prevalence
 130 in this population a modification of the DFT index was utilized. Wherein, caries scores were adjusted for
 131 the missing teeth, by dividing the total sum of decayed and missing teeth by the total number of teeth
 132 present in an individual. Therefore, this adjusted DFT is a continuous variable ranging from 0 to 1, with
 133 0 being the minimum caries experience and 1 being the highest (26).

134

135 **Results**

136 Fourteen study participants with OI type V underwent dental evaluation (Table 1). Panoramic
 137 radiographs were obtained in 9 study participants. None of the individuals had clinical or radiological
 138 signs of DI. Tooth discoloration, pulp obliteration, bulbous crowns, short roots or taurodontism were not
 139 observed in this cohort. Six of the nine study participants (55%) for whom panoramic radiographs were
 140 obtained had at least one missing tooth. The number of missing teeth ranged from 1 to 9. Three of these
 141 9 individuals had retained deciduous teeth past the normal range of exfoliation; eight study participants
 142 had impacted teeth. Ten study participants had an adjusted DFT score of 0, in four subjects the adjusted
 143 DFT score ranged from 0.21 to 0.67. Examples of the clinical and radiological features are shown in
 144 Figures 1 and 2.

145 All study participants had normal ear position and no frontal bossing (Table 3). The facial profile was
 146 retrusive in 8 of the 14 study participants (57%). Assessment of facial proportions showed decreased
 147 lower face height in 8 individuals (57%).

148 Cephalometry was performed in three study participants (Figure 3). Individual 9, a 14-year old girl,
 149 presented a severely retrusive maxilla and mandible, multiple missing teeth, an underdeveloped lower
 150 face and poorly angulated upper and lower incisors. In contrast, individual 10, a 14-year old boy, had a

protrusive maxilla and a retrusive mandible. Individual 13 presented with almost normal cephalometric results.

CBCT scans were obtained from two study participants. An impacted upper second molar and the absence of the lower third molars were detected in Individual 11 (not shown). In Individual 10, the CBCT scan demonstrated impacted second molars and semi impacted lower first molars. An intervertebral disc calcification at the C2-C3 level was also identified (Figure 4).

Discussion

In this largest dental and craniofacial study population reported to date, we found that DI was absent but that missing teeth, especially premolars was a common occurrence. Malocclusion associated with either a retrusive maxilla or biretrusive jaws was also frequently observed. The facial type was either normal or brachycephalic and more than half of the individuals with OI type V presented with a retrusive (concave) profile and decreased lower face height due to underdeveloped maxillary and mandibular dentoalveolar processes.

The absence of DI in OI type V has been reported in the first description of the disorder (10) and has also been noted in subsequent case series (16, 17, 27). This could be explained by the lack of a collagen type I defect in OI type V, as collagen type I is the major protein of intertubular dentin (90%) (28).

Previous reports have noted that missing teeth are a common finding in OI caused by *COL1A1/COL1A2*, affecting the permanent dentition in 10% to 22% of individuals (4, 29). Premolars appear to be most commonly affected (4). The present study suggests that premolars are also most frequently missing in OI type V. Tooth development is a complex process involving signaling pathways that are also important for skeletal development such as WNT signaling (30). It is therefore intuitive that genetic defects

173 leading to major abnormalities in bone cell function also affect tooth development, but the precise
 174 pathways whereby variants in *IFITM5* lead to tooth agenesis are unknown at present.

175 Previous studies have shown a high prevalence of class III malocclusion in the more severe OI types
 176 related to collagen type I mutations (OI types III and IV) (29, 31, 32). These malocclusions are caused
 177 by a severely hypoplastic maxilla and the counter rotation of the mandible resulting in severe negative
 178 overjet. Cephalometric studies suggest that the relative mandibular prognathism in these OI types in part
 179 reflects the decreased anterior length of the maxilla associated to a counterclockwise rotation of the
 180 mandible during growth (33). Our findings indicate that skeletal Class III malocclusion is less frequent
 181 in OI type V and that Class II malocclusion either of skeletal or dento alveolar origin is more frequent in
 182 OI type V than in other forms of moderate to severe OI. The severity of malocclusion varied widely in
 183 the present study independent of age. Six of the 14 study participants had severe malocclusion due to the
 184 presence of lateral open bite, multiple missing or impacted teeth and tooth migration. This indicates that
 185 their malocclusions presented significant therapeutic challenges where conventional orthodontic
 186 approaches would likely be inadequate. Nevertheless, the present study cohort presented with less severe
 187 malocclusion than what is typically seen in OI types III and IV caused by variants in *COL1A1* or
 188 *COL1A2* (5).

189 Regarding facial characteristics, reduced lower face height and concave profile were more common in
 190 our study cohort, suggesting that the dentoalveolar processes do not develop normally but do not result
 191 in the severely prognathic profile that is often observed in individuals with OI type II and IV. Deficient
 192 dentoalveolar development may be due to missing teeth altering the growth or may be a direct effect of
 193 the *IFITM5* variant.

194 In one of the two study participants who underwent CBCT scanning, we observed calcification of the
 195 intervertebral disk at the C2-C3 level. Calcification of intervertebral discs is a rare condition in children,

which may present with neck pain, limited neck movement or may be discovered incidentally as in the present case. The cause of intervertebral disk calcification is unknown, but trauma and infection have been suggested as likely causes (34). Intervertebral disk calcification can lead to disc herniation, dysphagia or spinal cord compression (35), but can also resolve spontaneously (34). Thus, further follow-up of this individual will be important.

In conclusion, our study observed that OI type V is associated with missing teeth but not with DI. Facial analyses and cephalometric data show that OI type V is characterized by dentoalveolar alterations due to multiple missing teeth but not an exaggerated overjet, as is frequently observed in other types of OI. The malocclusion phenotype of OI type V varies widely, similar to the wide range of bone abnormalities found in the postcranial skeleton (16). The malocclusion of OI type V, if present, could be described as a biretrusive maxillomandibular malocclusion with reduced lower face height and multiple missing teeth. OI type V thus is associated with a unique pattern of craniofacial abnormalities that differ considerably from the malocclusion of other forms of moderate to severe OI.

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310

311 **Figure Legends**

312

313 **Figure 1.** OI type V, Individual 9 (girl, 14 years). **A, B.** Intraoral photographs, showing posterior open
 314 bite, and Class III malocclusion. **C, D.** Occlusal view, showing missing premolars and retained lower
 315 deciduous molars. **E.** Panoramic radiograph, showing the deciduous molars with resorbed roots,
 316 unerupted 2nd molar (arrows), a missing lower incisor and the position of the 8 missing premolars
 317 (asterisks). Third molars are also congenitally missing (asterisks).

318

319 **Figure 2.** Individual 4 (girl, 8 years). **A, B, C** Intra-oral photographs, showing the anterior open bite
 320 with Class II malocclusion due to migration of upper permanent molars. **D.** Occlusal plane view. The
 321 radiograph shows the agenesis of the premolars (15, 25, 44, 34) as well as multiple impactions (12, 13,
 322 14, 24).

323

324 **Figure 3.** Cephalograms **A, B.** Individual 9 (girl, 14 years). The maxilla and mandible are significantly
 325 retrognathic. The ANB angle (-6.7 degrees, corresponding to 4.9 standard deviations [SD] below the
 326 reference mean value) and the Wits measurements (the length in mm of the yellow lines on the occlusal
 327 plane; 8.0 mm [3.1 SD above the reference mean value]) are abnormal, indicating a Class III biretrusive
 328 skeletal malocclusion compensated by severely proclined upper incisors (1 to NA line: 42.8 degrees;
 329 norm: 11 to 35 degrees) and severely retroclined lower incisors (lower incisor to mandibular plane
 330 angle: 67.8 degrees, norm: 83.4 to 99.4 degrees). The mandibular plane angle is also significantly
 331 decreased (15 degrees, norm: 25 to 41 degrees) indicating a severely brachycephalic facial type.

332 **C, D.** Individual 10 (boy, 14 years). Cephalogram reconstructed from cone beam CT. The mandible is
 333 retrognathic (the SNB angle is 74 degrees, reference mean 78 [SD: 3.0] degrees). The maxilla-

mandibular relationship is abnormal (the ANB angle is 7.4 degrees, reference mean 3.0 (SD: 2.0) degrees; Wits is 7.3, reference mean 2.0 [SD: 2.0] mm). All four second molars are impacted, the lower right first molar is semi-impacted and has only erupted partially. Roots on the lower left first molar are shortened. Typical Class II division 1 malocclusion with a retrognathic mandible and a reduced lower face height.

E, F. Individual 13 (47 year old male). Almost normal cephalometric measurements.

Figure 4. Cone Beam CT of Individual 10 (boy, 14 years). **A.** Three-dimensional volume rendering image. An unusual prognathic maxilla, impacted second molars (*) and lower right first molar is semi-impacted (arrowhead). **B.** Sagittal and **C.** Coronal images. There is a well-defined, round shaped radiopaque entity within the disc space at the C2-C3 level, consistent with intervertebral disc calcification (arrow). The adjacent vertebral end plates appear normal.

347 **Table 1. General clinical information and dental evaluation.**

Indi- vidual	Sex	Age (yrs)	Pan- orex	Missing teeth	Retained teeth	Impacted teeth	DFT
1	f	3	No	n.a.	n.a.	n.a.	0
2	f	4	No	n.a.	n.a.	n.a.	0
3	f	7	No	n.a.	n.a.	n.a.	0
4	f	8	Yes	15, 25, 34, 44	none	12, 13, 14, 24	0.21
5	m	8	No	n.a.	n.a.	n.a.	0
6	f	11	Yes	15, 24, 25, 31, 34, 35, 41, 44, 45	55, 73, 74, 83, 84	14	0
7	f	14	Yes	none	none	none	0.58
8	f	14	Yes	none	none	17	0
9	f	14	Yes	14, 15, 24, 25, 34, 35, 41, 44, 45	75, 85	17, 27, 37, 47	0
10	m	14	Yes	none	none	17, 27, 37, 46, 47	0
11	f	18	Yes	38, 48	none	17	0
12	f	41	Yes	15, 25, 34, 35, 45	none	27	0
13	m	47	Yes	35	none	28, 38, 48	0.67
14	m	50	No	Not available	none	none	0.40

348 Abbreviations: n.a., not available; DFT, decayed and filled teeth

349

350 **Table 2. Occlusion data.**

Individual	Molar occl right	Molar occl left	Canine occl right	Canine occl left	Severity of mal-occlusion	Over-jet (mm)	Over-bite (%)	Anterior cross-bite	Posterior cross-bite	Anterior open bite	Lateral open bite	Crowding
1	I	II	II	II	Mild	2	15	y	y	n	y	mild
2	II	I	II	I	severe	0	Openbite	y	y	y	y	n
3	I	I	I	I	mild	1	0	n	n	n	n	n
4	II	II	n.a.	n.a.	severe	-2	Openbite	y	y	y	n	mild
5	II	II	n.a.	I	mild	0	Openbite	y	n	y	n	mild
6	II	II	n.a.	n.a.	severe	4	100	n	y	n	n	n
7	I	I	I	I	mild	2	10	n	n	n	n	n
8	II	II	II	II	moderate	0	Openbite	y	y	y	n	n
9	II	II	III	III	severe	-1	0	y	y	y	y	n
10	II	II	II	II	severe	6	40	n	n	n	n	mild
11	I	I	I	I	n.a. (braces)	2	25	n	n	n	n	n
12	I	I	I	I	moderate	2	75	n	n	n	n	moderate
13	I	III	I	II	severe	0	Openbite	y	y	y	y	n
14	III	III	III	II	mild	2	25	n	y	n	y	mild

351 Abbreviation: n, no; n.a., not available; occl, occlusion; y, yes

Table 3. Facial characteristics.

Indi- vidual	Face Type	Facial Profile	H line	Z angle	Facial Proportions	Facial Proportions (%)
1	brachy	retrusive	7.8	76.9	normal	46
2	brachy	retrusive	Na	n.a	NA	na
3	normo	normal	19.1	70.4	normal	54
4	normo	retrusive	10.8	71.3	decreased LFH	45
5	normo	normal	24.5	59.3	Normal	52
6	brachy	retrusive	24.7	56.8	Normal	53
7	brachy	retrusive	3.7	78.3	decreased LFH	46
8	normo	normal	20.8	76.4	Normal	50
9	brachy	retrusive	0.1	91.8	decreased LFH	47
10	brachy	convex	24.6	65.8	decreased LFH	43
11	brachy	retrusive	11.2	76.8	normal	50
12	normo	retrusive	1.4	86.6	decreased LFH	43
13	normo	normal	6.1	88.6	Normal	47
14	normo	normal	9.3	99.9	normal	52

Abbreviations: LFH: lower face height; Normo: Normocephalic; Brachy: Brachycephalic

Figure 1

Figure 2

Figure 4