Published in final edited form as:

Am J Med Genet A. 2019 January ; 179(1): 65–70. doi:10.1002/ajmg.a.40383.

Dental and craniofacial characteristics caused by the p.Ser40Leu mutation in *IFITM5*

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Abstract

Severe forms of osteogenesis imperfecta (OI) are usually caused by mutations in genes that code for collagen type I and frequently are associated with craniofacial abnormalities. However, the dental and craniofacial characteristics of OI caused by the p.Ser40Leu mutation in the *IFITM5* gene have not been reported. We investigated a 15-year old girl with severe OI caused by this mutation. She had marked deformations of extremity long bones. There were no clinical or radiological signs of dentinogenesis imperfecta, but one tooth was missing and several teeth were impacted. Cone beam computed tomography revealed a generalized osteopenic appearance of the craniofacial skeleton, bilateral enlargement of mandibular bodies and areas of cortical erosions. The cranial base and skull showed a generalized granular bone pattern with a mixture of osteosclerosis and osteolysis. Sphenoid and frontal sinuses were congenitally missing. Cephalometric analysis indicated a class III growth pattern. In this case, the *IFITM5* p.Ser40Leu mutation did not affect tooth structure but was associated with deformities in craniofacial bones that resemble those in the other parts of the skeleton.

Keywords

Cone beam computed tomography; Craniofacial; Dental; Fractures; *IFITM5*

Introduction

Osteogenesis imperfecta (OI) is a heritable bone fragility disorder that can lead to markedly short stature, deformities of long bones, serial vertebral compression fractures and abnormalities of the craniocervical junction (Trejo & Rauch, 2016). Dental and craniofacial abnormalities such as dentinogenesis imperfecta (DI), tooth agenesis and malocclusion are also frequent (Andersson et al., 2017; Malmgren et al., 2017; Rizkallah et al., 2013) and specific craniofacial characteristics can be associated, including triangular face, protrusive bitemporal bone and prominent frontal bone (Waltimo-Siren et al., 2005).

In the large majority of cases, OI is caused by mutations in collagen type I encoding genes, but mutations in a number of other genes can also give rise to an OI phenotype (Forlino & Marini, 2016). OI type V is a disorder with specific phenotypic features such as hyperplastic callus formation and calcification of the interosseous forearm membrane (Cheung, Glorieux, & Rauch, 2007; Glorieux et al., 2000) that is caused by a single recurrent C>T transition at position -14 of the 5' untranslated region (p.(Met1ext-5)) of *IFITM5* (Bardai, Moffatt, Glorieux, & Rauch, 2016; Semler et al., 2012). *IFITM5* codes for a protein called BRIL that is found in the plasma membrane of bone-forming osteoblasts (Moffatt et al., 2008). The *IFITM5* p.(Met1ext-5) variant has been reported for more than 100 individuals with OI type V.

One other mutation in *IFITM5* (c.119C>T; p.Ser40Leu) has been observed that causes a severe dominant form of OI (Farber et al., 2014; Guillen-Navarro et al., 2014; Hoyer-Kuhn et al., 2014). The phenotype in the reported three individuals with this mutation included frequent fractures and long-bone deformities but not any of the characteristic clinical findings of OI type V, such as hyperplastic callus formation and calcification of the interosseous membrane. The 'correct' classification of the disorder is not clear, given that competing phenotype-based (Bonafe et al., 2015) and genotype-based (Forlino & Marini, 2016) classifications are used in the field. Based on genotype, the disorder caused by the *IFITM5* p.Ser40Leu mutation would be called 'OI type V'. However, as the phenotype is very different from the original description of OI type V (Glorieux et al., 2000) and bone histology shows a mineralization defect resembling that of OI type VI (which is usually caused by recessive *SERPINF1* mutations), the condition caused by the *IFITM5* p.Ser40Leu mutation has also been published under the label 'atypical OI type VI' (Farber et al., 2014).

Whatever the correct terminology, the craniofacial and dental phenotype associated with the *IFITM5* p.Ser40Leu mutation have not yet been documented in the literature. Here we describe the dental and craniofacial characteristics in a newly identified 15-year-old girl with the *IFITM5* p.Ser40Leu mutation.

Case Report

The proband was a 15-year-old girl who was assessed in the context of the Brittle Bone Disease Consortium study, (<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). The consortium is a Rare Disease Clinical Research Network that is funded by the National Institutes of Health. 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.). This patient was the first child of healthy non-consanguineous parents. Multiple fractures were noted during prenatal ultrasound examination. Postnatally she developed respiratory failure and eventually had a tracheostomy that was maintained until the age of 3 years. She continued to have fractures after birth and therefore received treatment with intravenous pamidronate infusions since the age of 6 months. Pamidronate infusions were given every 4 months until the age of 12 years, when intravenous zoledronate infusions (one infusion per year) were given instead, until the time of the present evaluation.

Since the age of 9 years she also received daily subcutaneous injections of growth hormone, which was continuing at the time of the study visit. Lower limb deformities were treated with intramedullary rodding procedures of both femurs and tibias at 18 months of age. These rods were subsequently exchanged several times.

Despite these interventions, she never walked independently. She is using a wheelchair for all mobility, but can transfer in and out of the wheelchair without help. She is physically active as a member of a school swim team and has excellent academic performance.

Sequence analysis of an OI gene panel including *COL1A1* (NM_000088.3), *COL1A2* (NM_000089.3), *BMP1* (NM_001199.3, NM_006129.4), *CRTAP* (NM_006371.4), *FKBP10* (NM_021939.3), *IFITM5* (NM_001025295.2), *P3H1* (NM_022356.3), *PLOD2* (NM_000935.2), *PPIB* (NM_000942.4), *SERPINF1* (NM_002615.5), *SERPINH1* (NM_001235.3), *SP7* (NM_152860.1), *TMEM38B* (NM_018112.2), *ALPL* (NM_000478.4), *CREB3L1* (NM_052854.3), *P4HB* (NM_000918.3), *PLS3* (NM_001136025.4), *RUNX2* (NM_001024630.3), *SEC24D* (NM_014822.2), *SPARC* (NM_003118.3) and *WNT1* (NM_005430.3) revealed a heterozygous c.119C>T (p.Ser40Leu) variant in *IFITM5*, which was confirmed by Sanger sequencing (Bardai et al., 2016). No pathogenic variants were found in the other genes. The *IFITM5* variant was not found in genomic DNA extracted from peripheral blood monocytes of both parents, suggesting that the mutation had occurred de novo in the patient. DNA analysis was not performed in the two unaffected siblings of the patient.

When the girl was evaluated at the age of 15 years, her height was 109.4 cm (z-score: -7.9) and weight was 38.5 kg (z-score -2.2). Sclera were white. Both upper and lower extremities were bowed. Pubertal development was at Tanner stage 3 for pubic hair and breast development, but menarche had not yet occurred. Audiological testing was normal. Pulmonary function testing showed that forced vital capacity was 103% of the result predicted for arm span (132 cm) and that forced expiratory volume in 1 second was 90% of the predicted result. Both results were considered normal. Dual-energy x-ray absorptiometry yielded a lumbar spine areal bone mineral density z-score of -0.3, which is close to the mean result for healthy controls of the same age and sex. Radiographs showed deformities and widening of long bones but no signs of hyperplastic callus formation or interosseous membrane calcification (Figure 1).

Material and Methods

The dental evaluation comprised clinical examination, extra- and intraoral photographs, panoramic radiograph, cone beam computed tomography (CBCT) scan and quality of life questionnaire. The presence of DI was evaluated both by clinical assessment of tooth color (opalescent, gray, brown or yellow color) and by examination of panoramic radiographs (criteria for DI were: partial or complete pulp obliteration, bulbous crown, cervical constrictions, roots abnormalities or short root, and taurodontism). Dental assessment also included the class of occlusion, overbite, overjet, crowding, openbite, crossbite and arch shape. Facial analysis was performed using lateral and frontal photographs to assess face symmetry, proportions and profile, as well as frontal bossing. CBCT scans were acquired

with a 3D Accuitomo 170 (Morita Inc, Kyoto, Japan) CBCT machine in a 170 mm × 120 mm field-of-view and a 250 µm 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 (Invivo Dental; Anatomage, San Jose, CA) software. Oral health related quality of life, was measured using the 20-item Oral Health Impact Profile (Allen & Locker, 2002).

Results

Clinical dental evaluation revealed absence of DI but presence of moderate dental crowding (Figure 2A). The patient was undergoing orthodontic treatment for anterior crossbite. This treatment had been started one year earlier and consisted of full upper and lower orthodontic brackets associated to a maxillary protractor. At the time of the present evaluation, the overjet was positive by 2 mm and there was no anterior or posterior crossbite. There was class III molar and canine malocclusion, a 5% lateral overbite but no anterior overbite. The Cone Beam CT showed that the upper incisors were severely proclined by the treatment, but the maxilla was still retrusive. In addition, the upper right lateral incisor had lost a significant amount of support on the lingual aspect of its root due to its excessive proclination. The panoramic radiograph revealed that the upper right third molar was congenitally missing, the upper left canine as well as all second molars were fully developed but had failed to erupt, pointing to probable impactions or very delayed eruption (Figure 2B). Facial evaluation showed a concave profile, normal facial proportions and absence of frontal bossing.

The CBCT showed a generalized osteopenic appearance of the gnathic structures, temporomandibular joints and cervical vertebrae (Figure 3). Bilateral enlargement of mandibular bodies was noted (Figure 3A). The inferior border of the mandible, buccal and lingual cortical plates in the posterior lower left mandibular quadrant (37) showed irregular areas of resorption along the inner cortical surfaces. The buccal cortical plate in the right mandibular body was irregularly eroded, more severely toward the ramus. The maxilla showed a granular trabecular bone pattern with some lytic areas (Figure 3B). The zygomatic process of the right maxilla was bulbous and showed a sclerotic granular bone pattern. Bilateral maxillary sinuses were hypoplastic and completely opacified. Both mandibular condyles showed loss of cortication in the articular surfaces and low bone density (Figure 3C). Enlargement of the right articular eminence was noted. The imaged portion of the cervical spine showed multiple, well-defined lytic areas consistent with subchondral cysts, loss of cortication and reduced bone density (Figure 3D). Sphenoid and frontal sinuses were congenitally missing. Mucosal swelling was noted in the ethmoid sinuses. There was reduced bone support on the proclined maxillary incisors but an absence of root resorption (Figure 3E). The cranial base and skull showed generalized granular bone pattern with a mixture of osteosclerosis and osteolysis (Figure 3F).

Cephalometric analysis of the CBCT scan revealed that transverse and vertical dimensions were all within normal limits, but the elevated Bjork's beta angle indicated a class III growth pattern (Figure 4). The saddle angle, which is frequently reported as abnormal in OI (Waltimo, Ojanotko-Harri, & Lukinmaa, 1996), was within normal limits.

The oral-health related quality of life questionnaire did not reveal any negative issues. The patient reported no problems with her dental condition except for some episodes of mild discomfort.

Discussion

Here we report for the first time the dental and craniofacial phenotype associated with the *IFITM5* p.Ser40Leu mutation. We found no clinical or radiological signs of DI, but one tooth was missing and there were several impacted teeth. At the same time, we observed major deformities in the craniofacial skeleton with lack of cortical definition. This is similar to the severe deformities that were also present in the long bones of this individual.

The overall phenotype of the girl presented here is in accordance with the three reported individuals who had OI caused by the p.Ser40Leu mutation in *IFITM5* (Farber et al., 2014; Guillen-Navarro et al., 2014; Hoyer-Kuhn et al., 2014). Fractures and bone deformities occurred already in utero and postnatal growth was severely restricted. Despite her extreme short stature (109 cm), she was considerably taller than the previously reported adult with the p.Ser40Leu mutation (height: 87 cm) (Farber et al., 2014), which may be due to the early start of bisphosphonate therapy, treatment with growth hormone, other environmental influences or genetic differences in genes other than *IFTIM5*.

The absence of DI could be related to the absence of a defect in collagen type I, which is the major protein of intertubular dentin (Goldberg, Kulkarni, Young, & Boskey, 2011). DI is also absent in individuals with the *IFITM5* c.-;14C>T mutation (Glorieux et al., 2000). Previous reports have noted that missing teeth are a common finding in OI, affecting the permanent dentition of 10% to 22% of individuals with mutations in collagen type I encoding genes (Malmgren et al., 2017; O'Connell & Marini, 1999). Our observations suggests that missing teeth can also be a feature of the *IFITM5* p.Ser40Leu mutation. Previous studies have also shown a high prevalence of class III malocclusion in severe OI caused by mutations in genes encoding collagen type I (Chang, Lin, & Hsu, 2007; O'Connell & Marini, 1999; Schwartz & Tsipouras, 1984). Class III malocclusion was also observed in the present study participant but was relatively mild and was associated with crowding and impacted teeth.

At the time of our investigations, the study participant had completed one year of orthodontic treatment with the goal of aligning the dentition and correct the skeletal class III malocclusion. This resulted in a positive overjet but in a severe proclination of the upper anterior teeth, while the maxilla was still retrusive. Furthermore, the bony quality and remodeling potential of the temporomandibular joints may not be adequate for the use of a mandibular protractor that places significant stress on these structures. These observations highlight the difficulties of orthodontic therapy in patients with severe bone fragility disorders. Care should be exercised to avoid deleterious effects on the skeletal tissues and periodontal tooth support. The treatment response of bony structures may not be as favourable as in patients with normal bone quality.

The bone pattern alterations revealed by the CBCT examination have some resemblance with those found in other diseases, such as panostotic or polyostotic fibrous dysplasia where granular trabecular bone structure, cortical thinning with endosteal erosion and bony expansion are also observed (Cole et al., 1983). Juvenile Paget's disease may also show mixed osteolytic and sclerotic lesions of the skull (Whyte et al., 2002). Severe hypophosphatasia is characterized by reduced trabecular bone density, thinning of cortical bone, enamel hypoplasia, large pulp chambers and root canals (Whyte, 2016). Even though these disorders are caused by defects in other genes, the partial overlap in clinical features with the individual presented here could indicate that they share some pathogenetic pathways with those activated by the *IFITM5* p.Ser40Leu mutation.

The p.Ser40Leu mutation in *IFITM5* is associated with bone histological abnormalities resembling those in OI type VI caused by *SERPINF1* mutations (Farber et al., 2014). Similar to the patient presented here, individuals with OI type VI do not have DI. The craniofacial phenotype of OI type VI has not been reported. However, in the context of the ongoing Brittle Bone Disease consortium study we have performed CBCT on three adolescents and young adults with OI type VI and did not find major abnormalities (unpublished observation), which contrasts with the marked craniofacial bone deformities that we observed in the individual presented here.

Bisphosphonates are widely used in children with OI, to increase bone strength and reduce fracture rates (Trejo & Rauch, 2016). Among the potential complications of long-term bisphosphonate treatment is bisphosphonate-related osteonecrosis of the jaws, which is characterized by an area of ulcerated mucosa with exposed necrotic bone. This complication has not been observed in children with OI (Hennedige, Jayasinghe, Khajeh, & Macfarlane, 2013) and in the present individual, there was no clinical or radiographic evidence of exposed necrotic bone. Radiographically, the resorption along the inner cortical surfaces at site 37, inferior border of mandible and right mandibular body-ramus and osteolytic trabecular bone may be considered a risk for developing osteonecrosis of the jaw. The radiographic appearance at these sites is also consistent with increased risk of pathologic fracture.

The major limitation of the present report is the fact that only a single case is described. We are therefore not able to conclude whether the presented craniofacial phenotype is typical for individuals with the *IFITM5* p.Ser40Leu mutation.

In conclusion, the present report of an individual with *IFITM5* p.Ser40Leu mutation did not identify any abnormalities in tooth structure but was associated with severe deformities in craniofacial bones that resemble those in the other parts of the skeleton.

Acknowledgments

We are grateful to Jane Atkinson (National Institutes of Health) for helpful suggestions. This study was performed as an activity of the Brittle Bone Disease Consortium. The Brittle Bone Disease Consortium (1U54AR068069-0) is a part of the National Center for Advancing Translational Sciences (NCATS) Rare Diseases Clinical Research Network (RDCRN), and is funded through a collaboration between the Office of Rare Diseases Research (ORDR), NCATS, the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and the National Institute of Dental and Craniofacial Research (NIDCR). The content is solely the responsibility of the authors and

does not necessarily represent the official views of the National Institutes of Health. The study was also supported by the Shriners of North America. None of the authors declares a conflict of interest.

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Figure 1.

Skeletal radiographs in a 15-year-old girl with a heterozygous *IFITM5* p.Ser40Leu mutation.

A, B. Skull. The cortex of the parietal bones appears ill-defined. **C, D.** Spine. The anteroposterior view (C) shows mild scoliosis. On the lateral view (D), there are no clear vertebral fractures, but there are several cystic areas in the vertebral bodies. There is hyperlordosis and the sacrum is deformed. **E, F.** Lower extremities. Both femurs and tibias have undergone intramedullary rodding surgery. Diaphyses are wide, cortices are ill-defined and there are cystic areas. **G, H.** Upper extremities. The abnormalities are similar to the lower extremities. **I.** Hand. Cystic changes in the metacarpal and phalangeal bones.

Figure 2.

A. Clinical dental appearance. Class III malocclusion with 5% overbite and moderate dental crowding but absence of dentinogenesis imperfecta. **B.** Panoramic radiograph, reconstructed from CBCT. Impacted teeth 17, 23, 27, 37 developing teeth 18, 28, 38 and missing tooth 48.

Figure 3.

CBCT images. R: Right L: Left **A.** Bilateral enlargement of mandibular bodies and resorption of buccal and lingual cortical plates (arrows). Presence of osteolytic areas (asterisk). **B.** Hypoplastic right maxillary sinus with complete opacification (arrow). The maxilla shows a granular trabecular bone pattern with some lytic areas (arrowhead). **C.** Loss of cortication in the articular surfaces of the mandibular condyles and decreased bone density (asterisk), as well as enlargement of the right articular eminence (arrow). The bulbous zygomatic process of right maxilla shows sclerotic granular bone pattern (double arrowhead). Lack of frontal sinus (arrowhead). **D.** Multiple, well-defined lytic areas consistent with subchondral cysts in the cervical spine (arrow) and reduced bone density. **E.** Maxillary incisors are proclined and have reduced bone support, but there is no evidence of root resorption. **F.** The skull has a generalized granular bone pattern with a mixture of osteosclerosis and osteolysis (arrows). Presence of ethmoid sinusitis (asterisk). Lack of sphenoid sinus (arrowhead).

Figure 4. Cephalometric analysis of the CBCT scan. The beta angle is defined as the angle between the subspinale (A) - supramentale (B) line and the perpendicular to the Condylion (Co)-B line. A beta angle above 35 degrees indicates a class III growth pattern (Baik & Ververidou, 2004). The result here is 38 degrees, indicating a class III pattern.