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Expanding the phenotypic spectrum of osteogenesis imperfecta type V including heterotopic ossification of muscle origins and attachments

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Abstract

Background: Osteogenesis imperfecta (OI) is a clinical and genetic heterogeneous group of connective tissue disorders, characterized by bone fragility and a propensity to fracture.

Methods: In this report we describe the clinical phenotype of two patients, a 28-year-old woman and her mother (54 years old), both with a history of short stature and multiple fractures.

Results: Exome sequencing revealed the recurring *IFITM5*:c.-14 C>T variant causing OI type V. Both patients had several fractures during childhood. CT-scan and scintigraphy showed ossification of the origin and attachment of muscles and hypertrophic callus formation.

Conclusion: Ossification of the origin and attachment of muscles seems to be part of the phenotype in patients with OI type V.

KEYWORDS

BRIL, heterotopic ossification, *IFITM5*, Osteogenesis imperfecta type V

1 | INTRODUCTION

Osteogenesis imperfecta (OI) is a heterogeneous connective tissue disorder, with severity ranging from mild osteoporosis to perinatal lethality (Sillence, 1988; Sillence & Rimoin, 1978). The cardinal symptom is bone fragility predisposing to fractures, short stature, and bone deformity. Low bone mineral density is generally observed, and extra-skeletal manifestations, such as blue sclera and dentinogenesis imperfecta (DI), may also be present. Hearing impairment in OI has been reported as well, and is caused by conduction defects in the middle ear and sensorineural hearing loss later in life (Sillence, Rimoin, & Danks, 1979). Dominant mutations in collagen type I (Sillence, Rimoin, et al., 1979), the main component of skeletal extracellular matrix, are responsible for 85%–90% of cases (Lindahl et al., 2015), and in recent years numerous recessive, dominant, and X-linked genes have been associated with noncollagen-related OI (Marini et al., 2017).

Glorieux et al. (2000) described a novel form of OI in 2000 (OI type V), observed in seven patients with an autosomal dominant pattern of inheritance (Glorieux et al., 2000). The reported children with OI type V had moderate to severe bone fragility. None of the patients had clinical signs of DI or blue sclerae. Histological examination of bone biopsies revealed irregular pattern of the lamellae. Subsequently, individuals with a clinical presentation of OI type V have been found to have highly variable phenotypes, even within the same family, carrying the same mutations. However, the common skeletal phenotype

includes: calcification of the forearm interosseous membranes, radial head dislocation, subphyseal-metaphyseal radiodense lines, and hyperplastic callus formation (HCF; Cheung, Azouz, Glorieux, & Rauch, 2008; Strach, 1953; Vieira et al., 2006). Most cases of OI type V are caused by a pathogenic heterozygous variant interferon-induced transmembrane, (*IFITM5*: c.-14C>T) in the 5'-UTR of *IFITM5* (Cheung, Glorieux, & Rauch, 2007). In this case report we describe two subjects, and provide new phenotypic information on OI type V.

2 | PATIENTS AND METHODS

2.1 | Subjects

A 28-year-old female of North Macedonian origin was referred to the department of clinical endocrinology at Uppsala University Hospital for investigation of suspected skeletal dysplasia in March 2014. Clinical and genetic evaluation was performed by a multidisciplinary team including endocrinologists, orthopaedic surgeons, clinical geneticists, and radiologists. The Regional Ethical Review Board at Uppsala University, Uppsala, Sweden, approved the study (2017-390-32M). Subjects have given their written informed consent to participate in the study.

2.2 | Molecular genetic evaluation

DNA was extracted from whole blood using an automated robot system (QIAcube system, QIAGEN). First DNA was sent to Emery Genetics Laboratory, Georgia, USA, for sequencing of 173 genes associated with skeletal dysplasia, and later to Blueprint genetics, Helsinki, Finland, for copy number variation (CNV) analysis of 173 genes. Exome sequencing was performed at Uppsala Genome Centre, Uppsala, Sweden, using the Ampliseq (Life Technologies) and Ion Proton system (Life Technologies). Data filtering was performed, excluding variants with frequencies of >1% in the in-house curated Canvas database (github.com/ UppsalaGenomeCenter/CanvasDB; Ameur, Bunikis, Enroth, & Gyllensten, 2014). Variant annotation information was obtained from dbSNP137 (Sherry et al., 2001) and ANNOVAR (Wang, Li, & Hakonarson, 2010). The generated VCF-files were analyzed using the Moon software from diploid (http://www.diploid.com) using the HPO term "Osteopenia" to search for known disease associated variants or genes. The identified variant in *IFITM5* was validated using Sanger sequencing on gDNA from the index patient and her mother. The *IFITM5* variant was amplified using a standard PCR reaction (available upon request).

2.3 | Case history

The 28-year-old woman was born three weeks prematurely; her length was 46 cm (±0 *SD*) and weight 2,460 g (±0 *SD*). The final height of the index patient was 152 cm (−2.5 *SD*).

Her first fracture occurred in the forearm when she was 2.5 years old, and she had several subsequent fractures in the forearm, but none after the age of 12. In childhood she suffered from chronic back pain with onset at an age of 2–3 years. The patient received a treatment with antiresorptive medication (probably bisphosphonate) at the age of 12, with some clinical improvement for 2–3 years. Radiographs of the spine and pelvis at that time indicated osteopenia and revealed fishbone-like, biconcave thoracic and lumbar vertebrae, and multiple ossification of the origins of large muscle groups at the upper and lower anterior iliac spine.

At the time of referral, the patient complained of chronic back pain as well as pain in the right hip and right lower leg, which limited the level of activities and physical exercise. The patient had been smoking during the past 8–9 years (five cigarettes per day) and she reported an alcohol consumption corresponding to one bottle of wine per week. The patient denied abdominal pain, weight loss, and diarrhea.

The family history revealed that the patient's mother (54 years old) had suffered from multiple forearm fractures during adolescence and reached a final height of 160 cm (−1 *SD*). She was diagnosed with osteoporosis and treated with regular injections of denosumab twice a year. No investigation of bone metabolism or underlying genetic disorders was performed during her childhood or adolescence. The grandparents of the index patient have no history of fractures or short stature supporting the presence of a de novo mutation in the index patient's mother.

3 | RESULTS

3.1 | Clinical report

The final height of the index patient is 152 cm, the arm span 155 cm, sitting height 75 cm, and head circumference 53.5 cm. Her forearms are curved, and she has an elbow extension defect, and has hyper extensible joints. Physical examination did not reveal blue sclerae or DI.

Basal laboratory investigation showed a normal sedimentation rate, a blood hemoglobin of 153 g/L (ref. 120–150 g/L) and normal platelet and white blood cell rates. Plasma sodium, potassium, creatinine, alkaline phosphatase, TSH, ALT, and AST were normal as well. Serum phosphate was 0.75 mmol/L (ref. 0.80–1.5 mmol/L). Plasma electrophoresis showed normal immunoglobulin fractions. Serum parathyroid hormone was 3.8 pmol/L (ref. 1.6–6.9 pmol/L), and 25-OH-D-vitamin 35 nmol/L (ref. >25 nmol/L). A Dual-energy X-ray absorptiometry (DXA scan) showed a *Z* score of −1.1 *SD* (ref. ≥−2) in the spine, and 1.1 *SD* (ref. ≥−2) in the hips. Lateral vertebral radiography revealed biconcave vertebrae in the lumbar and distal thoracic spine.

Plain anteroposterior and axial radiography of the pelvis and hips showed no gross osteopenia but robust cortical bone

in visible parts of the femora, progression of the above-mentioned ossification of the muscle origins around the pelvis, and additionally ossifications corresponding to the attachment of the adductor muscles along the linea aspera bilaterally. Joint space narrowing and osteophyte formation, indicative of osteoarthritis, were observed in both hip joints. A computed tomography of the spine showed multiple biconcave thoracic and lumbar vertebra. A subsequently performed whole-body computed tomography (Figure 1a) showed bilateral ossification of the attachment of the deltoid muscle at the humeral deltoid tuberosities and ossification of multiple muscle origins at the superior and inferior anterior iliac spine, of the origins of the gluteus medius muscles bilaterally, of the adductor muscle origins bilaterally, and at the iliac crests at the origins of the quadratus lumborum muscles bilaterally (Figure 1b). Furthermore, ossification of the adductor muscle attachments at the posterior femoral diaphysis along the linea aspera (Figure 1c), and bilateral ossification of the soleus muscle origins at the dorsal proximal tibial meta-diaphysis (Figure 1d and 1e).

The total body computed tomography also showed diaphyseal curvature of both forearms with interosseous membrane ossification, and radial head subluxation on the right side (Figure 1a).

Interosseus membrane ossification between tibia and fibula was also seen bilaterally. Bilateral acetabular protrusion with enhanced coverage of the femoral head and bilateral osteoarthritis of the hips was also found (Figure 1b).

A total body scintigraphy was performed with a SPECT/DT, and revealed multiple sites of uptake in the skeleton, corresponding to the HCF previously seen on computed tomography.

3.2 | Molecular genetic evaluation

A comprehensive skeletal dysplasia panel and CNV analysis (173 genes) did not identify a pathogenic sequence/CNV variant. DNA from the index patient and her mother was used for exome sequencing and analysis of exome data revealed a previously known pathogenic variant situated in the 5' UTR of*IFITM5*, NM_001025295.2: c.-14C>T in both affected women.

4 | DISCUSSION

Osteogenesis imperfecta type V has a unique clinical and extremely variable phenotype. Herein we expand the OI type V phenotypic spectrum of a 28-year-old woman including multiple, symmetric heterotopic ossification of muscle origins and attachments. The index patient in this study has short stature, curved right forearm with HCF, and extension defect of the elbows. She also has ossifications of the origin and attachment of muscles and tendons including intraosseous membranes, and bilateral coxarthrosis. HCF of the forearm was present, probably secondary to previous fractures.

Heterotopic ossification (HO) is the phenomenon of pathologic bone formation. HO is the consequence of several conditions which include acquired and hereditary forms. Acquired forms include central nervous system insults (such as traumatic brain injury and spinal cord injury), and other conditions including trauma and surgery (Garland, 1991). A genetic predisposition HO has been verified as well, and hereditary forms include fibrodysplasia ossificans progressiva (Kaplan et al., 2005) and progressive osseous heteroplasia (Kaplan et al., 1994). Its clinical presentation may be characterized by edema, pain, and stiffness (Zychowicz, 2013). HO of the muscle origins and attachments has been previously described in the muscles and tendons attached to the pelvic bone and femur in OI type V. Kim et al. (2013) described four patients with heterotopic ossification of the femur, acetabulum, and iliac crest, similar to those seen in patients with myositis ossificans or fibrodysplasia ossificans progressiva. In contrast to the patients reported by Kim et al. the index patient presented in this case developed ossifications at the spinae iliacae anteriores superiores et inferiores, of the origins of the gluteus medius muscles bilaterally, of the adductor muscle origins bilaterally, and at the cristae iliacae at the origins of the quadratus lumborum muscles bilaterally.

Occurrences of HCF have previously been described (Battle & Shattock, 1908) and were sometimes misdiagnosed as osteosarcoma, a differential diagnosis of HCF (Koskinen, 1958; Vieira et al., 2006). However, cases of osteosarcoma arising in patients with OI are very rare (Maiya, Grimer, Ramaswamy, & Deshmukh, 2002; Takahashi et al., 2004). Hyperplastic callus formation may arise following a fracture, a surgical procedure, or as a spontaneous development. By far, the femur is the most affected bone, followed by the tibia, humerus and forearm bones (Burchardt, Wagner, & Basse, 1994; Strach, 1953). A majority of patients with OI type V have ossifications of the interosseous membrane of the forearm and radial head dislocation, and HCF is reported in approximately 65% (Shapiro et al., 2013).

Several strategies have been studied as management of HCF. Immobilization with radiological follow-up (Apley, 1951), adrenocorticotropic hormone- or radio-therapy (Maiya et al., 2002) at early stages, have been proposed. Current knowledge dictates a conservative approach with symptomatic treatment and frequent follow-up. While bisphosphonate therapy is the standard of care for most forms of OI (Dwan, Phillipi, Steiner, & Basel, 2016), there is limited information regarding the effects of the therapy on HCF, which is an integral component of OI Type V. In a study by Cheung et al. (2007), in 23 patients with type V OI, pamidronate therapy was not found to influence the course of HCF. In another study of 11 patients with type V OI, the response to pamidronate treatment was found to be the same as in other types

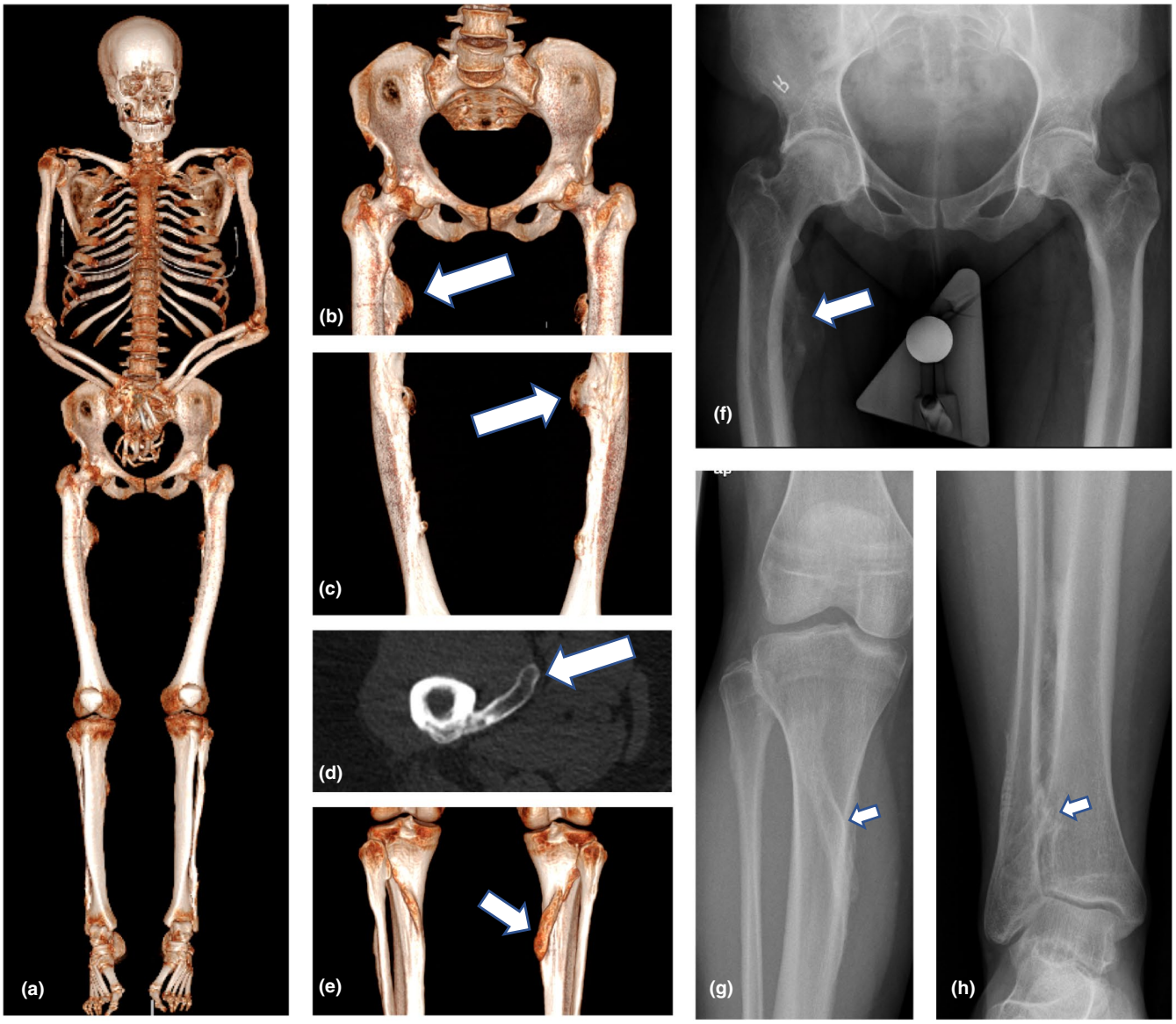

FIGURE 1 (a) Three-dimensional reconstruction of total body computer tomography scan showing heterotopic ossification of muscle origins and attachments. Bilateral ossification of the attachment of the deltoid muscle at the humeral deltoid tuberosities. Diaphyseal curvature of both forearms with interosseous membrane ossification, and radial head subluxation on the right side. (b) Pelvic skeleton, anterior view of 3D reconstruction. Ossification of multiple muscle origins at the spinae iliacae anteriores superiores et inferiores, of the origins of the gluteus medius muscles bilaterally, of the adductor muscle origins bilaterally, and at the cristae iliacae at the origins of the quadratus lumborum muscles bilaterally. Bilateral acetabular protrusion with enhanced coverage of the femoral head and bilateral osteoarthritis of the hips. Arrow pointing at ossification at the insertion of the right adductor muscles. (c) Femoral bones, posterior view of 3D reconstruction. Bilateral ossification of the adductor muscle attachments at the posterior femoral diaphysis along the linea aspera. Arrow pointing at ossification at the insertion of the right adductor muscles. (d) Coronal section through right femur. Ossification of the insertion of the adductor magnus muscle along the linea aspera (arrow). (e) Tibial bones, posterior view of 3D reconstruction. Bilateral ossification of the soleus muscle origins at the dorsal proximal tibial meta-diaphysis. Arrow pointing at ossification at the origin of the right soleus muscle. (f) Conventional radiography of the pelvis, anteroposterior view. Arrow pointing at ossification at the insertion of the right adductor muscles. (g) Conventional radiography of right tibia, anteroposterior view. Arrow pointing at ossification at the origin of the right soleus muscle. (h) Conventional radiography of right tibia, anteroposterior view. Arrow pointing at ossification of the interosseous membrane and the syndesmotic tibiofibular ligaments

of OI (Zietlin, Rauch, Travers, Munns, & Glorieux, 2006). Exacerbation of HCF on treatment with bisphosphonates has been observed in one study (Ranganath, Stephen, Iyengar, & Phadke, 2016). The exacerbation was chronologically related to, and thus attributable to the initiation of bisphosphonate therapy. Our patient reported a good clinical response, but no radiological evaluation was available in order to assess the baseline condition and response to treatment.

As mentioned before, most cases of OI type V are caused by a pathogenic heterozygous variant (*IFITM5*:c.-14C>T) in

the 5'-UTR of *IFITM5*, which encodes a transmembrane protein enriched in osteoblasts during mineralization (Moffatt et al., 2008). The pathogenic OI type V variant introduces an alternative start codon and putatively adds five amino acids to the N-terminus of BRIL (Semler et al., 2012). *Ifitm5* has been studied in mice and rats and, in these animals, *Ifitm5* expression peaks during osteoblast maturation around the early mineralization stage, suggesting a role in bone formation (Hanagata et al., 2011; Hanagata, Takemura, Monkawa, Ikoma, & Tanaka, 2007; Moffatt et al., 2008). *Ifitm5* overexpression in UMR106 cells and primary rat osteoblasts resulted in a dose-dependent increase in mineralization, whereas knockdown of *Ifitm5* by shRNA in MC3T3 osteoblasts induced reduced mineralization (Moffatt et al., 2008). *Ifitm5* knockout mice and *IFITM5* transgenic mice do however not exhibit major bone abnormalities (Hanagata et al., 2011).

A transgenic mouse model of OI-V expressing the *IFITM5*:c.-14C>T variant (Lietman et al., 2015) exhibited slow rate of mineralization in utero, abnormal rib cage formation, long bone deformities and fractures. Furthermore, growth plate expansion was also observed, as seen in infant patients with OI-V. The degree of mineralization is reduced as well, suggesting a role of *IFITM5*:c.-14C>T variant in osteogenesis. The different observations in vitro and in vivo suggest that loss of function of *IFITM5* alone could not explain all phenotypic characteristics.

Reich et al. (2015) observed a gain-of-function in mineralization, which could be related to the overactive tissue mineralization seen in patients with OI type V, and explain part of the observations of Kim et al. (2013). However, this observation suggests excess mineralization and contradicts bone fragility seen in the same patients. Cho et al. (2012) hypothesized that this contradictory effect on the phenotype may be caused by a site-specific dysregulation of bone formation. Further research is required in order to elucidate and confirm these findings.

5 | CONCLUSION

Ossification of the origin and attachment of muscles is part of the phenotype in patients with OI type V, along with the previously described HCF, calcification of the forearm interosseous membrane, and radial head dislocation.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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