Bone 110 (2018) 66–75

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Case Report

# Novel variant in Sp7/Osx associated with recessive osteogenesis imperfecta with bone fragility and hearing impairment

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ARTICLE INFO

*Article history:*
Received 11 December 2017
Revised 24 January 2018
Accepted 25 January 2018
Available online xxxx

*Keywords:*
Osteogenesis imperfecta
*SP7/Osx*
Osterix
Fractures
Hearing impairment

ABSTRACT

Osteogenesis imperfecta (OI) is a connective tissue disorder characterized by low bone density and recurrent fractures with a wide genotypic and phenotypic spectrum. Common features include short stature, opalescent teeth, blue sclerae and hearing impairment. The majority (>90%) of patients with OI have autosomal dominant variants in *COL1A1/COL1A2*, which lead to defects in type 1 collagen. More recently, numerous recessive variants involving other genes have also been identified. *Sp7/Osx* gene, is a protein coding gene that encodes a zinc finger transcription factor, osterix, which is a member of the Sp subfamily of sequence-specific DNA-binding proteins. Osterix is expressed primarily by osteoblasts and has been shown to be vital for bone formation and bone homeostasis by promoting osteoblast differentiation and maturation. In animal models, *Sp7/Osx* has also been shown to regulate biomineralization of otoliths, calcium carbonate structures found in the inner ear of vertebrates. Until recently, only one report of a boy with an *Sp7/Osx* pathogenic variant presenting with bone fragility, limb deformities and normal hearing has been described in the literature. We have identified a novel *Sp7/Osx* variant in another sibship that presented with osteoporosis, low-trauma fractures and short stature. Progressive moderate-to-severe and severe-to-profound hearing loss secondary to otospongiosis and poor mineralization of ossicles and petrous temporal bone was also noted in two of the siblings. A homozygous pathogenic variant in exon 2 of the *Sp7/Osx* gene was found in all affected relatives; c.946C>T (p.Arg316Cys). Bone biopsies in the proband and his male sibling revealed significant cortical porosity and high trabecular bone turnover. This is the second report to describe children with OI associated with an *Sp7/Osx* variant. However, it is the first to describe the bone histomorphometry associated with this disorder and identifies a significant hearing loss as a potential feature in this OI subtype. Early audiology screening in these children is therefore warranted.



## 1. Introduction

Osteogenesis imperfecta (OI) is a clinically heterogeneous genetic brittle bone disorder with features including fragility fractures, bone pain, impaired growth, low bone density and other musculoskeletal and systemic anomalies. Furthermore, when the ossicles or temporal bones are affected, hearing impairment can arise. The vast majority of OI is caused by autosomal dominant variants in type 1 procollagen genes, *COL1A1* (MIM 120150) and *COL1A2* (MIM 120160). In the last two decades genes responsible for recessive OI have been described that encode for proteins responsible for post-translational modification, trafficking, processing or secretion of type 1 collagen [1] or are involved in the formation and homeostasis of bone tissue. *Sp7/Osx* (MIM 606633) located at 12q13.13 [2] encodes the 431 amino acid transcription factor osterix which has three tandem zinc-finger DNA-binding domains and belongs to the specificity protein (Sp) family [3]. Osterix amplifies the expression of other osteoblast markers such as osteonectin, osteopontin, bone sialoprotein and osteocalcin [3,4]. Recently, it was also demonstrated that osterix up-regulates the expression and activity of connexin

*Abbreviations:* BMI, body mass index; DXA, dual-energy x-ray absorptiometry; Cx43, connexin 43; OI, osteogenesis imperfecta; pQCT, peripheral quantative computerized tomography; SDS, standard deviation score.

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https://doi.org/10.1016/j.bone.2018.01.031
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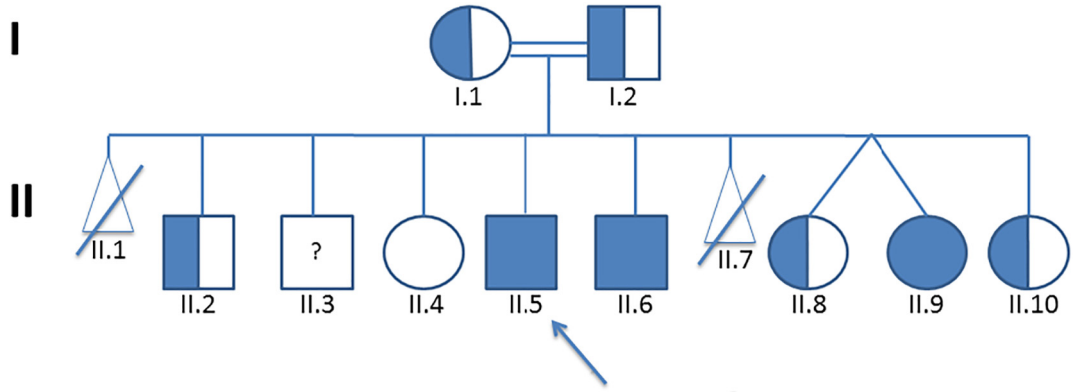


**Fig. 1.** Family pedigree. The proband (arrow; II.5) and two other children (II.6 and II.9) with a similar phenotype were homozygous for the *SP7/Osx* variant. Both parents (I.1 and I.2) carried the variant in the heterozygous state and unaffected siblings either did not carry the pathogenic variant (II.4) or carried it in the heterozygous state (II.2, II.8). The triangles indicate 2 separate pregnancies that ended in spontaneous abortion. Genetic testing was unavailable for one family member (indicated by "?" in II.3).

43 (Cx43) [5], a gap-junction protein known to regulate osteoblastic function [6–9]. Nakashima et al. (2002) were the first to demonstrate that *Sp7/Osx* is crucial for bone development and exerts its effects downstream from Runx2, another transcription factor essential for bone formation. In *Sp7/Osx* null murine embryos, bone formation is absent due to a lack of osteoblasts differentiation [3]. Known roles of *Sp7/Osx* include: [1] osteoblast differentiation and maturation during embryonic bone formation, [2] maintenance of adult bone in mammals [3,10] and [3] regulation of chondrocyte differentiation and maturation [11].

The first and only report of recessive OI associated with a *Sp7/Osx* variant in a family describes one affected member with recurrent fractures, mild bone deformities, delayed tooth eruption, normal hearing and white sclera [1]. Other groups have described associations between common variants in the region around *Sp7/Osx* and bone mineral density in childhood [12]. Furthermore, the expression and function of *Sp7/Osx* in non-skeletal tissue has been described in animal models [13,14]. However, there is a paucity of human clinical data relating to recessive OI and *Sp7/Osx* variants.

This report describes the phenotype and genotype of three individuals from a family found to have a novel homozygous variant in *Sp7/Osx* leading to recessive bone fragility, impaired growth and hearing loss.

## 2. Patients and methods

### 2.1. Patients

#### 2.1.1. Proband

The proband (II.5) was the 4th of eight children born from an uncomplicated pregnancy to healthy consanguineous parents of Iraqi descent (Figs. 1, 2). There were no perinatal issues and psychomotor development progressed normally. Between 5 and 10 years of age, his

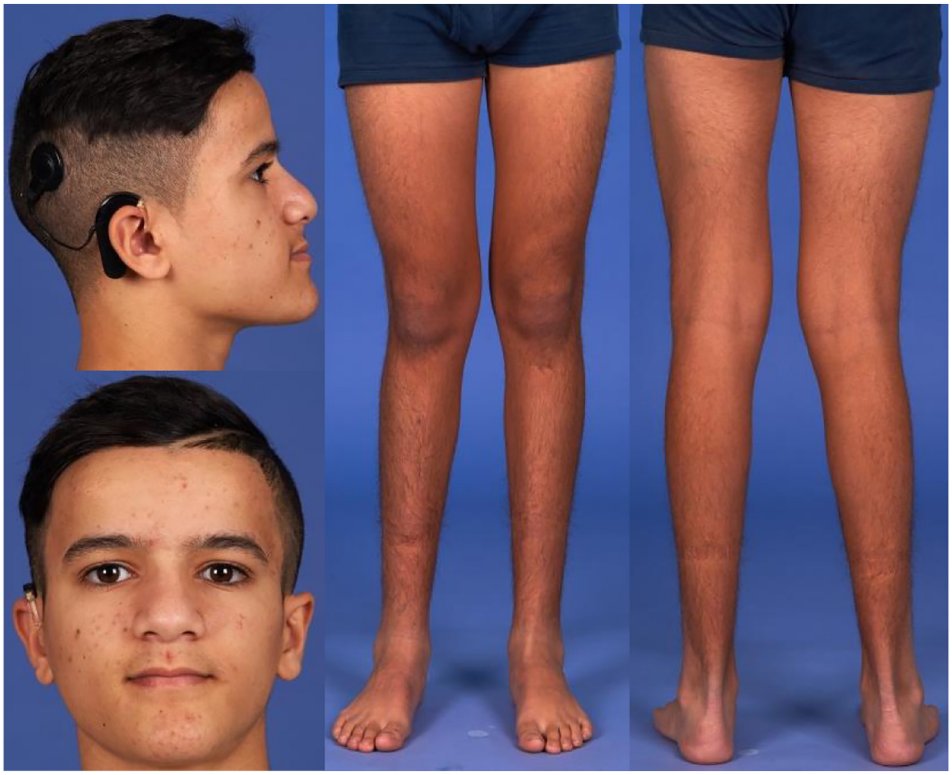

**Fig. 2.** Proband phenotype. Clinical aspects of proband at 16 years of age.