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Mutations in IFITM5 leading to prenatal and postnatal signs of dominant Osteogenesis imperfecta

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Conclusion

- **Dominant mutations in the non-coding region of IFITM5 are connected to the clinical hallmarks of moderate OI V.**
- **We report the first mutation in the coding region of IFITM5 leading to a complete different phenotype with severe OI with prenatal onset.**
- **In patients suspected of OI, the entire gene IFITM5 – and not only the 5´-UTR region– has to be analyzed to exclude a causal role of IFITM5.**
- **IFITM5 influence differentiation of osteoblasts via the protein BRIL demonstrating a new pathophysiology causing OI.**

Background

Osteogenesis imperfecta (OI) is a hereditary disease with high variability of clinical symptoms, formerly associated with autosomal dominant mutations in *COL1A1/A2.* Recently a widening range of recessive mutations has been discovered. Most mutations cause alterations in the posttranslational modification of collagen. Recently, a heterozygous mutation in the 5´-untranslated region of IFITM5 (c.-14C>T) was identified as the cause of dominant OI type V (1).

Objective

Three children of healthy parents presenting with symptoms of OI with increased fracture rate and reduced bone mass were examined. Analysis of *COL1A1/A2* genes and the known recessive genes for OI revealed no mutations. The objective was to determine the underlying genotype and comparing the phenotype of OI in these 3 children.

Patients

We describe 3 patients from 3 families with extremely different phenotypes. Patients presented at the age of 19 months / 8.7 years and at birth. They showed no signs of a pathologic collagen production (dentinogenesis imperfecta, hypermobility of joints, discoloured sclera). Serum calcium and alkaline phosphatase levels were normal. Further characteristics are displayed in Tab 1.

	Patient 1	Patient 2	Patient 3
Sex	female	male	male
Disease severity	moderate	moderate	severe
Skeletal findings			
Prenatal fractures of extremities	no	no	yes
Age at first fracture (months)	5	18	0
Hyperplastic callus	yes	yes	no
Bowing of upper extremities	no	no	yes
Bowing of lower extremities	no	no	yes
Shortening of upper extremities	no	no	yes
Shortening of lower extremities	no	no	yes
Other findings			
Color of sclera	white	white	white
Dentinogenesis imperfecta	no	no	no
Hypermobility of joints	no	no	no
Hearing impairment	no	no	no
Intellectual development	normal	normal	normal
Therapy			
DXA ap spine at start (z-score)	-3.3	-2.8	Not available
Deoxypyridinoline / creatinine (osteoclast marker) [nM/mM] first visit (Reference range)	58.66 (6.5-26.5)	63.9 (13.1-51.0)	58.24 (6.5-6.5)
Bisphosphonate treatment start (years)	1.7	9.9	0.1
***IFITM5* Mutation**	c.-14C>T	c.-14C>T	c.119C>T

Table 1: Clinical and laboratory characteristics of patient 1 - 3

Methods

To identify the underlying genotype whole-exome sequencing was used after informed consent was given.

Results I - Clinical

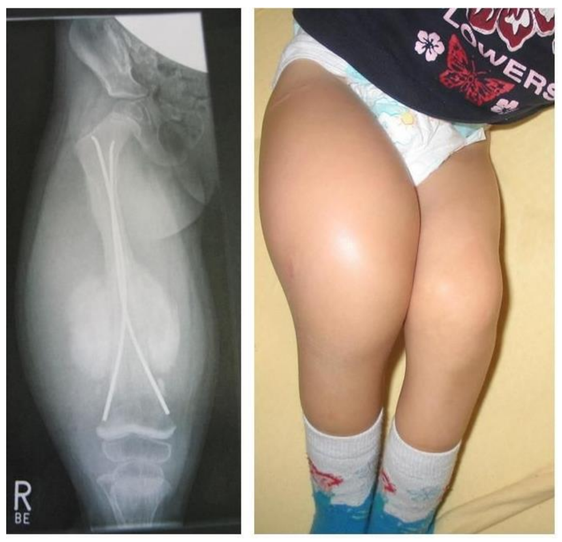

Fig 1:
Hyperplastic callus formation in patient 1

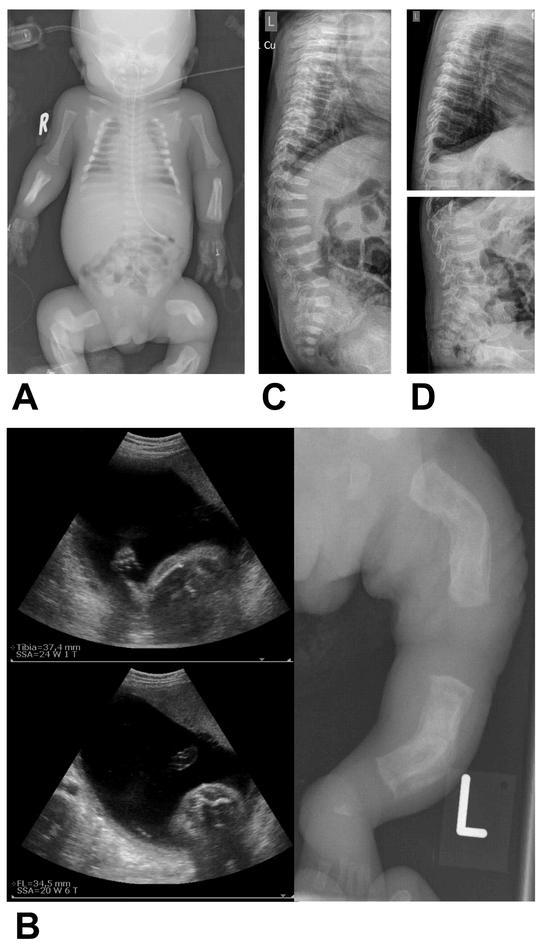

Fig 2:
Skeletal prenatal and postnatal findings of patient 3.
A) Radiograph revealing intrauterine fractures. B) Ultrasound picture presenting prenatal bowing and shortening of tibia and femur; Postnatal radiograph showing old fractures, C) and D) Lateral view of the spine with 6 months / 19 months after bisphosphonate treatment.

Results II - Genetical

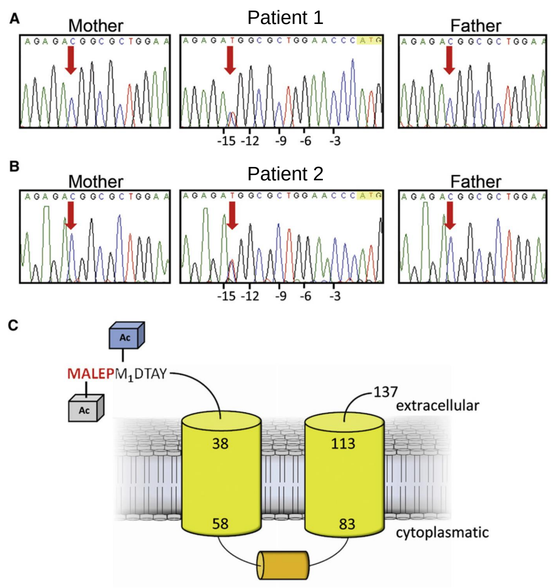

Fig 3:
Patient 1/2 : A de novo-mutation in the 5´UTR region of IFITM5, c.-14C>T, was found (A/B). This creates an in frame start codon adding five amino acids (red in C) before the transmembrane domains 1/2 (TMD1/TMD2).

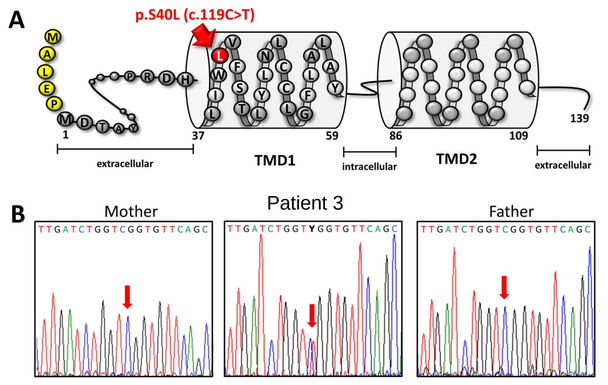

Fig 4:
Patient 3: The described *IFITM5* mutation of patient 1/2, c.-14C>T, which is located in the 5'-UTR (yellow), was excluded. A heterozygous mutation within the coding region of *IFITM5* (c.119C>T; p.S40L) was found (2).
A) Pearl necklace-like representation of the IFITM5 protein. The discovered mutation in the first transmembrane domain is highlighted in red.
B) Sanger sequencing of the heterozygous IFITM5 mutation.

Abbreviations: OI (Osteogenesis imperfecta), DXA (Dual energy x-ray absorption)

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Disclosure statement: No author has a conflict of interest

References: 1. A mutation in the 5´-UTR of IFITM5 creates an in-frame start codon and causes autosomal dominant osteogenesis imperfecta type v with hyperplastic callus. Semler O, Garbes L, et al: Am J Hum Genet. 91(2):349-57.
2. A nonclassical IFITM5 mutation located in the coding region causes severe osteogenesis imperfecta with prenatal onset. Hoyer-Kuhn H, Semler O, Garbes L, Zimmermann K, Becker J, Wollnik B, Schoenau E, Netzer C. J Bone Miner Res. 2014 Jun;29(6):1387-91.