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**Article:**

Redman, M.G., Wagner, B.E. and Balasubramanian, M. (2020) Osteogenesis Imperfecta type I : the role of deep phenotyping in a patient with a ruptured uterus. *European Journal of Medical Genetics*, 63 (12). 104095. ISSN: 1769-7212

<https://doi.org/10.1016/j.ejmg.2020.104095>

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# **Osteogenesis Imperfecta type I: the role of deep phenotyping in a patient with a ruptured uterus**

## **Authors**

Melody Grace Redman<sup>1,2</sup>, Bart E Wagner<sup>3</sup>, Meena Balasubramanian<sup>1,2</sup>

1 - Sheffield Children's NHS Foundation Trust, Sheffield, UK

2 - University of Sheffield, Sheffield, UK

3 - Histopathology Department, Royal Hallamshire Hospital, Sheffield, UK

## **Corresponding author**

Dr Meena Balasubramanian, Sheffield Children's NHS Foundation Trust, Western Bank, Sheffield S10 2TH E-mail: [meena.balasubramanian@nhs.net](mailto:meena.balasubramanian@nhs.net)

## **Word count**

1424 words

## **Acknowledgement**

Thank you to the patient for permitting us to share this information, and to all the staff who were involved in the care of the patient and her family.

## **Funding**

This report explores findings from a skin biopsy which was funded through the RUDY (Rare Diseases in Bone, Joints and/or Blood Vessels) study, by the NIHR Rare Diseases Translational Research Collaboration.

## **Competing interests**

The authors have no competing interests to declare.

## **Consent**

The patient gave explicit written consent for the case to be written as a clinical report.

## Abstract

As molecular diagnosis of Osteogenesis Imperfecta has become more accessible, there is an increasing ability to consider additional techniques to undertake deep phenotyping of the patient.

In this report, we present the details of a female patient with type I Osteogenesis Imperfecta caused due to a pathogenic *COL1A1* variant, who suffered from uterine rupture during labour in her second pregnancy, at age 33. Her presentation, patient journey, and histological results are described. Collagen flowers were identified with electron microscopy of a skin biopsy, and the significance of these are explored. Two other recorded cases of women with Osteogenesis Imperfecta who developed uterine rupture are discussed.

This report demonstrates the potential role for ultrastructural tissue examination and deep phenotyping, to allow further insights into the relationship between genotype and phenotype.

## Keywords

(max 6)

osteogenesis imperfecta

*COL1A1/COL1A2*

collagen flowers

type 1 collagen

phenotype

uterine rupture

## **Background**

Osteogenesis imperfecta (OI) is a spectrum of hereditary disorders, commonly referred to as 'Brittle Bone Disease'. This is one of the more common 'rare' disorders, affecting one in 15,000-20,000 births.[1] Type I collagen, a protein family which is necessary for normal bone structure, is affected. The primary feature displayed by patients is a propensity to low trauma fractures. However, collagen is also found in many other body tissues; defective collagen, therefore, may be implicated in other disease manifestations. Some patients with OI may demonstrate the classic findings of blue sclerae and hearing loss, and the cardiorespiratory system may also be affected, with reduced pulmonary function and valvular regurgitation.[1]

**Table 1 – Type of OI, pattern of inheritance, and genetic aetiology [2,3]**

Type of OI	Pattern of inheritance	Genetic aetiology
I	Autosomal Dominant (AD)	<i>COL1A1 or COL1A2</i>
II	AD	<i>COL1A1 or COL1A2 or CRTAP</i>
III	AD	<i>COL1A1 or COL1A2</i>
IV	AD	<i>COL1A1 or COL1A2</i>
V	AD	<i>IFITM5</i>
VI	Autosomal Recessive (AR)	<i>SERPINF1</i>
VII	AR	<i>CRTAP</i>
VIII	AR	<i>P3H1</i>
IX	AR	<i>PPIB</i>
X	AR	<i>SERPINH1</i>
XI	AR	<i>FKBP10</i>
No type	AR	<i>PLOD2</i>
XII	AR	<i>BMP1</i>
XIII	AR	<i>SP7</i>
XIV	AR	<i>TMEM38B</i>
XV	AR or AD	<i>WNT1</i>
XVI	AR	<i>CREB3L1</i>
XVII	AR	<i>SPARC</i>
XVIII	X-linked recessive	<i>MBTPS2</i>

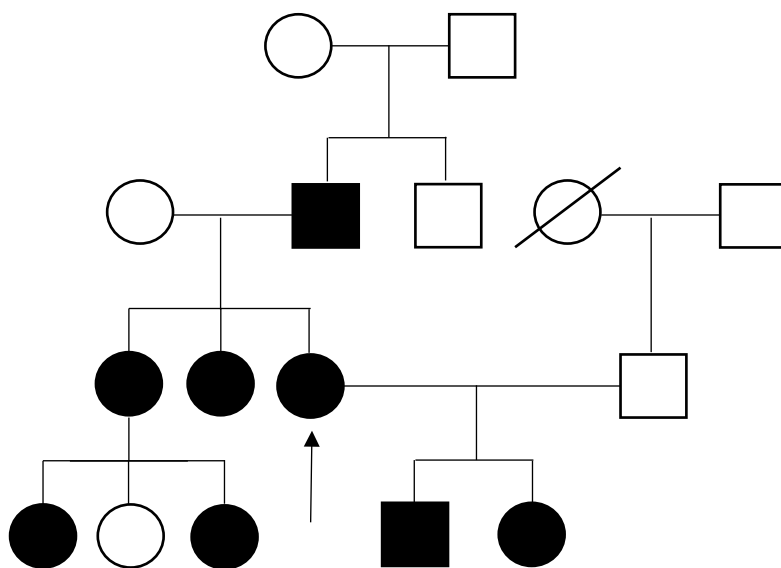
Table 1 demonstrates the inheritance pattern and genetic aetiology of the different types of OI. Most patients with OI have pathogenic variants in *COL1A1* or *COL1A2* which follows an autosomal dominant pattern of inheritance.[1] The first recessive gene was identified in

2006,[3] but since then both autosomal recessive and X-linked recessive inheritance have been described on several occasions.[4-6] There were initially four clinical phenotypes described by Sillence in 1979,[7] and this system of classifications was amended in 2014.[8]. Phenotypic variability is a well-recognised aspect in OI. We currently do not have a precise mechanism to predict the severity that a family member may demonstrate. A previous study demonstrated the role for undertaking clinical and molecular phenotyping by assessing skin biopsies from patients.[9] Here, we describe an adult female with an inherited variant in *COL1A1*, who developed a uterine rupture during pregnancy, and the role of deep phenotyping alongside genomic analysis.

### ***Clinical report***

An adult female initially presented with her partner to the Genetics clinic at age 33. She was referred from the Metabolic Bone Medicine team, for recurrence risk discussion as there were several of her family members known to have type I osteogenesis imperfecta (OI). Her father, both of her two sisters, and one niece, had mild OI, but another niece was quite severely affected and phenotypically thought to have type IV OI [see Figure 1]. The patient herself had a history of congenital dislocation of the hip (both hips, but right worse than left), and a fractured tibia at 7 years of age (requiring manipulation under anaesthetic) following a fall from a bike. She also had a history of a radial fracture, and several toe and finger fractures. She underwent right hip replacement at 25 years of age. She had a history of hearing loss in both ears, and had a right-sided hearing aid. She had bluish-grey sclerae and her teeth appeared normal; there were no other relevant findings. She was under regular follow up and on regular Adcal D3 but never had bisphosphonate treatment. Although several members of the family carried the same variant and had phenotypic similarities with fractures and blue sclerae, one member had been phenotypically diagnosed as type IV OI whilst the patient reported here was phenotypically labelled as type I OI.

**Figure 1 – Family tree of patient, demonstrating inheritance pattern. All shaded shapes are those affected with osteogenesis imperfecta.**



Due to suspected OI, advice was provided, where the autosomal dominant inheritance pattern and the 1 in 2 chance of having an affected child, with variable severity, was explained. The patient was exploring in vitro fertilization (IVF) due to primary infertility. No cause had been identified for the infertility despite several investigations for this. The patient and her partner were informed of various options available in conjunction with IVF, including prenatal genetic testing, donor egg and pre-implantation genetic diagnosis (PGD). The patient decided not to pursue PGD and proceeded with IVF.

Within a short window of time, the patient became pregnant, and was seen again at 15 weeks of pregnancy. Results confirming a pathogenic c.2644C>T variant in *COL1A1* were given: NM\_000088.3(COL1A1):c.2644C>T (p.Arg882Ter). This pathogenic variant was predicted to replace the arginine at position 882 with a premature termination codon and had previously been reported in individuals with OI type I and IV. Prenatal invasive testing, including chorionic villus sampling and amniocentesis to check if the pregnancy was affected, were discussed and declined by the patient.

The patient's familial variant is documented in the Leiden OI Variant Database (#0001616).[10] Of the nine patients noted to have the same variant in the OI variant database, only one is listed as having type IV OI (which is the younger patient in this family

with a more severe phenotype). This is likely due to phenotypic characterisation rather than genotype. It is likely that the mechanism of clinical presentation with this variant is haploinsufficiency.

The son of the patient was born at 37 ½ weeks via emergency C-section for maternal pre-eclampsia and breech presentation. He weighed 2.6kg (2<sup>nd</sup>-9<sup>th</sup> centile). He required a 2-day admission to the special care baby unit for treatment of jaundice and received phototherapy, fluid and intravenous antibiotics. He was exclusively breastfed and developmentally normal, with bluish sclerae. Buccal samples were taken with consent to check whether he had OI, and he was found to carry the same familial *COL1A1* variant. Advice around careful handling was given and he was referred to Metabolic Bone Services, where he remains under follow-up. He had a mild degree of plagiocephaly and had sustained fractures of his tibia aged 2.5 years and mild loss of height (T4/T5 vertebrae) which is being monitored.

The patient then went on to naturally conceive a second child shortly after. A cleft lip and palate was detected following her 20 week scan and a subsequent 4D scan. At 37+1 weeks, the baby girl was born. The labour was distressing and difficult. The uterus and bladder were ruptured, although the baby girl was immediately well after birth via category 1 caesarean section, weighing 2.4kg (2<sup>nd</sup> centile). Feeding was successfully established and cleft lip surgery was planned and undertaken at 12 weeks of age. On examination, the baby girl did not demonstrate any clinical features of OI, but a diagnostic array CGH was requested due to cleft lip and palate (this demonstrated a female profile with no clinically significant imbalance), and predictive testing for OI was requested, where the same *COL1A1* variant was seen.

Due to the history of uterus and bladder rupture in the second delivery, the patient was discussed in adult bone multi-disciplinary team, and it was agreed to request a skin biopsy as part of the RUDY (Rare Diseases in Bone, Joints and/or Blood Vessels) study. The patient consented to this procedure; skin biopsies were taken for further analysis including electron microscopy and culturing fibroblasts.

## **Results**

Electron microscopy of the skin biopsy revealed flower-like cross sections and twisted rope-like longitudinal sections of collagen fibrils [see Figures 2-4], ranging from 90nm up to 886nm. The smaller flowers were moderately frequent. The patient had significantly smaller

than expected mean collagen fibril diameter of 65nm (expected = 80nm). The packing of collagen bundles was not uniform; scattered spaces were present.. Elastic fibres appeared unremarkable.

**Figures 2-4: Transmission Electron Microscopy images of thin section UA/Pb stained abnormal collagen fibrils 'collagen flowers' within collagen bundles in mid reticular dermis.**

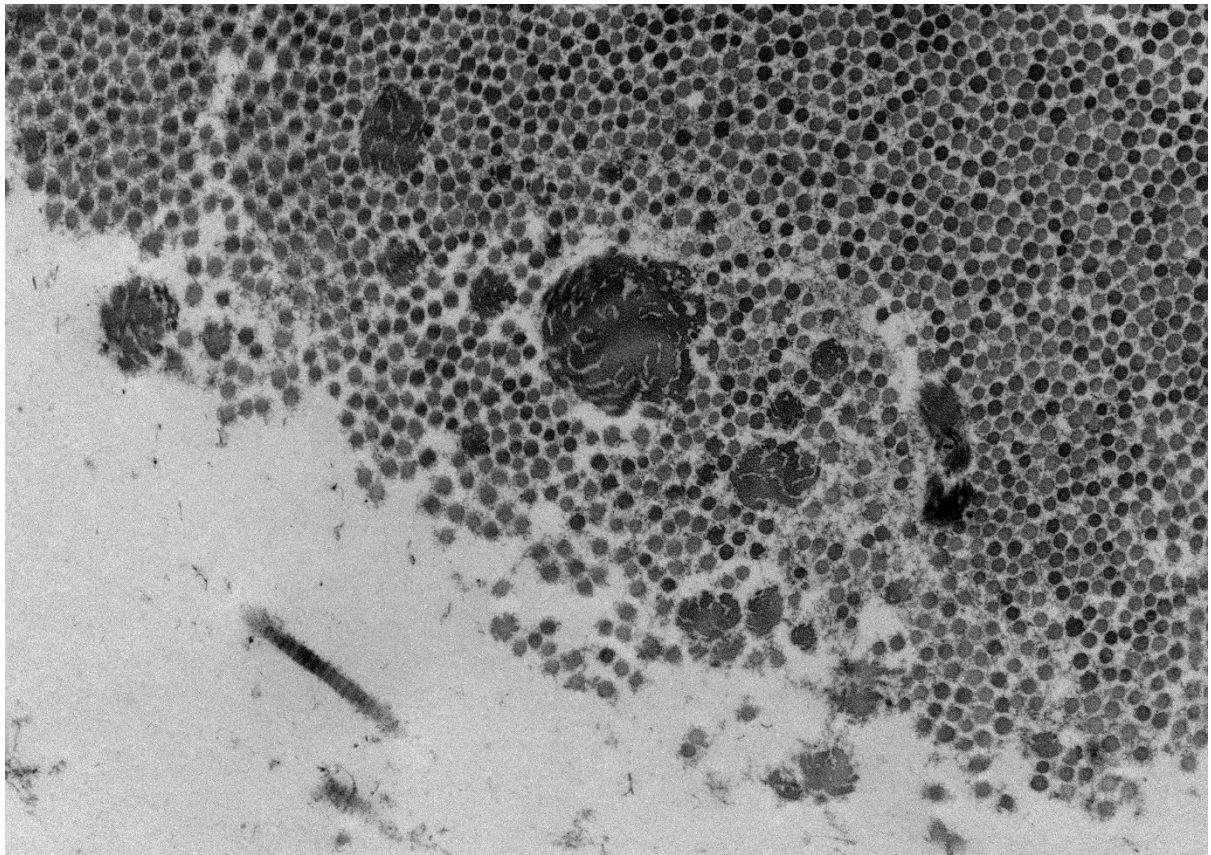


Figure 2: Transverse sectional orientation. Original magnification x9,200

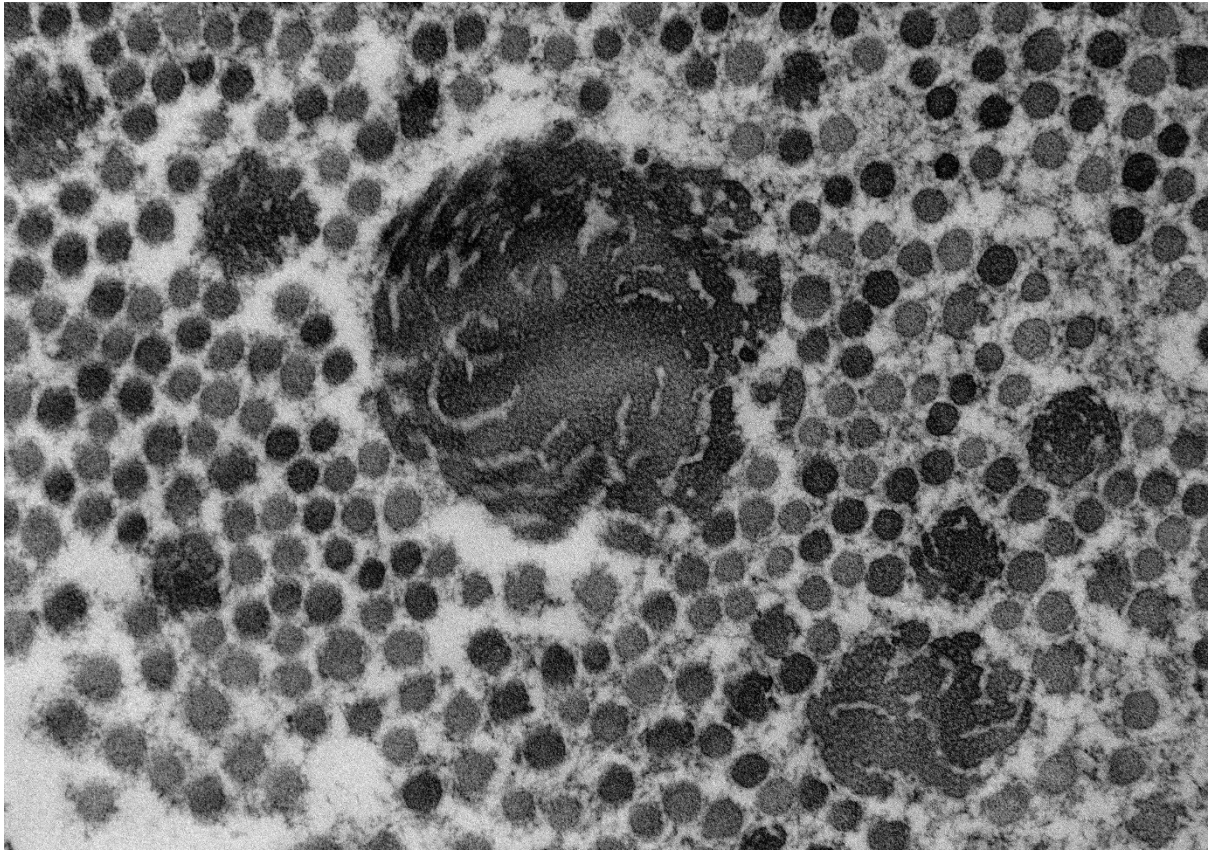


Figure 3: Same area as previous. Original magnification x20,000

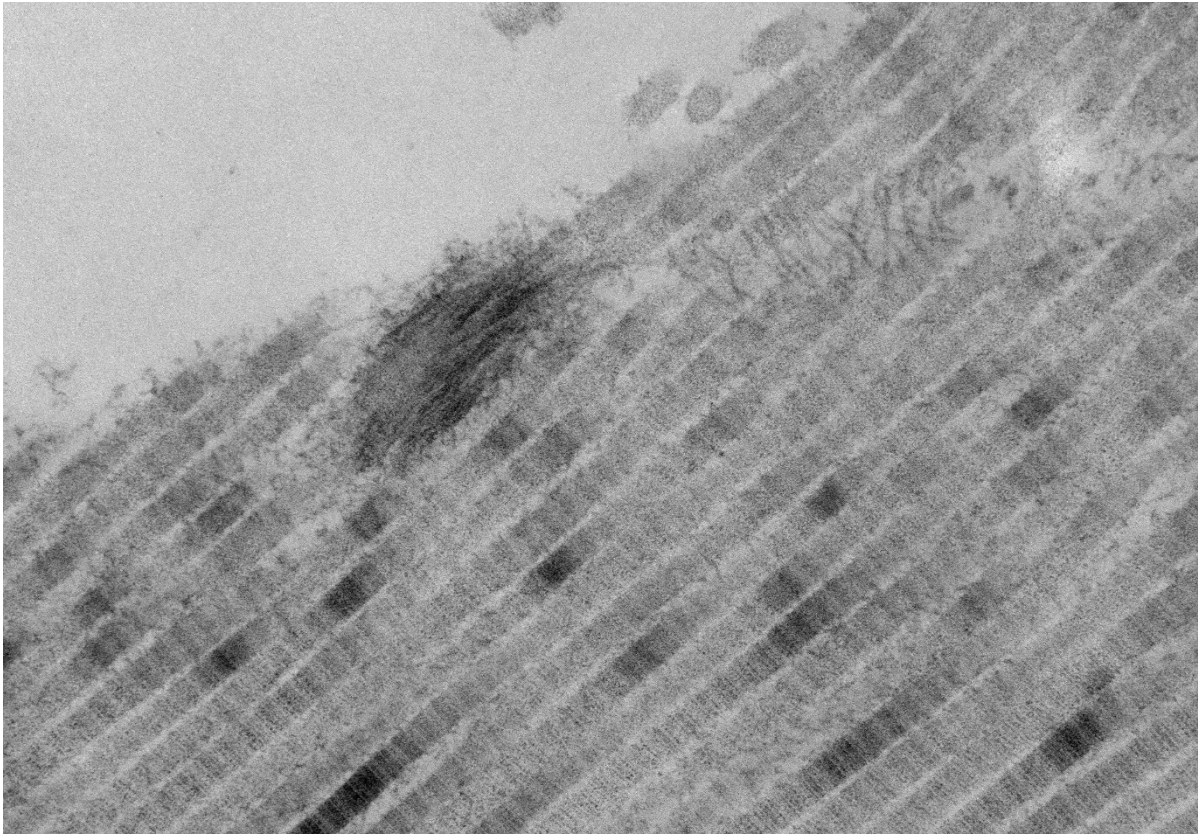


Figure 4: Longitudinal section of a different collagen bundle containing a small collagen flower. Original magnification x20,000

## Discussion

A range of pregnancy complications have been experienced in women with OI.[11] Uterine rupture has been described in two other women with OI.[12-14] Young et al [12, p.467-468] describe that a 32-year-old pregnant lady (gravida 2, para 1) presented in 1966, had a clinical diagnosis of OI, and a medical history which included syphilis and intravenous heroin use. She had sustained multiple fractures since she was 2 years old. The patient had spontaneous onset of labour and rupture of membranes. The baby was spontaneously delivered at 6 hours and 17 minutes of labour and was well. Sadly, the lady developed a 5cm uterine rupture, leading to excessive bleeding, deterioration, and death, despite medical and surgical intervention. Histological examination of the uterus showed defective collagen.[12]

A patient report published in 2002 by Krishnamoorthy et al [13] discussed a 24-year-old woman with type I OI who presented in her second pregnancy. She had previous childhood

fractures of the ulna, radius, and phalanges, and had a molecular diagnosis of *COL1A1* variant.[14] In her first pregnancy, she had undergone a suction termination at 8 weeks' gestation.[13] In her second pregnancy, she presented in established labour at full term, with 6cm cervical dilatation. After a further 6 hours with no progression of labour, it was decided to proceed with a caesarean section. At that time, a 3cm uterine rupture was noted. A 2.3kg well boy was delivered, and the rupture was repaired.[13] The same woman presented later with a further pregnancy, and an elective caesarean section was scheduled at 39 weeks gestation, at which point a biopsy was also taken, with prior consent.[14] The biopsy was compared to a control patient who had a repeat elective caesarean section at 39 weeks. The patient with a history of uterine rupture and OI was noted to have a reduction in the amount of collagen, a reduction in the amount of type 1 collagen which surrounded the muscle fascicles, and an overall increase in the amount of muscle and the amount of type 3 collagen.[14]

Electron microscopy of our patient's skin biopsy demonstrated multiple collagen flowers, which is typical for a connective tissue disorder. As OI is a type 1 collagen disorder, and therefore a connective tissue disorder, this was not a surprising finding. Histological findings in other patients have also demonstrated elastic fibres with clumping and fragmentation.[9] Balasubramanian et al [9] demonstrated that some patients with *COL1A1* variants, similar to this patient, also have collagen flowers. Holbrook & Byers observed collagen flowers in patients with type I OI, as well as in patients with other connective tissue disorders.[15] In patients with *COL5A1/A2* gene variants, classical Ehlers–Danlos syndrome, it has been suggested that as the number of collagen flowers increase, the severity of the clinical phenotype and symptoms perhaps also increases.[15-17] Ultrastructural examination of the skin may be a useful investigation to understand more about the clinical phenotypes of patients.

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