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Diagnostic conundrums in antenatal presentation of a skeletal dysplasia with description of a heterozygous C-propeptide mutation in COL1A1 associated with a severe presentation of Osteogenesis Imperfecta



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Keywords:	COL1A1, Osteogenesis Imperfecta, high bone mass phenotype, C-propeptide cleavage site
Search Terms:	Osteogenesis Imperfecta, Bone fragility, Bone mass, COL1A1

SCHOLARONE™
Manuscripts

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4 Subject: AJMG - MS 16-0094 Revision Required
5

6 Dear Prof Hennekam,
7

8 Thank you for considering our manuscript 'A Heterozygous C-propeptide
9 Mutation in COL1A1 Associated with a Severe, Antenatal Presentation of
10 Osteogenesis Imperfecta' which has been reviewed for the American Journal
11 of Medical Genetics.
12

13
14 I have addressed the comments raised by the reviewers and hope the revised
15 manuscript meets your approval. We have also added to the clinical
16 description. I hope you are able to consider our work favourably.
17

18 **Please could I have a favourable decision prior to my Fellowship**
19 **deadline of 15th August as it would be great to add this manuscript to my**
20 **Fellowship application! Many thanks.**
21

22
23 Sincerely,
24

25 Meena Balasubramanian
26 Consultant in Clinical Genetics
27 Lead Consultant, OI-Genetics Service, Highly Specialised Severe, Complex &
28 Atypical OI Service
29 Honorary Senior Clinical Lecturer, Dept. of Human Metabolism, University of
30 Sheffield
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36 Title: A Heterozygous C-propeptide Mutation in COL1A1 Associated with a
37 Severe, Antenatal Presentation of Osteogenesis Imperfecta
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39 Response to Editor's Comments:
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41
42 Your manuscript has been evaluated by one of the Original reviewers who
43 was in general pleased with the way you have adapted the manuscript. I
44 concur. The reviewer still has a few remarks, which do need attention. In
45 addition I noticed that some of the references are incomplete, and none of the
46 references have used the international abbreviations of the journal's names
47 (as can be found in PubMed). Please check the guidelines for authors on the
48 site and.
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50
51 *Response: Sincere apologies for this, corrected references in manuscript*
52 *according to author instructions.*
53

54 Please resubmit the manuscript with a rebuttal letter mentioning all issues
55 raised by reviewer and editor, and how you have incorporated these into the
56 manuscript. I will re-evaluate the manuscript thereafter myself. If adequately
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3 changed I shall then be pleased to advise the Editor-in-Chief to accept the
4 manuscript.

5
6 *Response: Thank you.*

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8 Response to Reviewer Comments:

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10 Reviewer: 1

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12 Comments to the Author

13 This draft of the manuscript reads much better than the first draft, and I would
14 suggest only a few minor edits.

15
16 *Response: Thank you.*

17
18 1) Pamidronate is capitalized in a couple of places, but should not be unless
19 at the start of a sentence.

20
21 *Response: Apologies, corrected.*

22
23 2) I would recommend that since this article is submitted to the American
24 Journal of Medical Genetics, that spelling be per standard American English.

25
26 *Response: Apologies, corrected.*

27
28 3) Although I appreciate the nuance in the discussion of termination in
29 patients with potentially lethal skeletal dysplasias, there was one sentence
30 that I disagreed with. The authors still imply that termination is still the only
31 sensible option in some cases. While we as genetics personnel may believe
32 this, non-directive counselling is still important and I might suggest that the
33 authors alter this wording accordingly.

34
35 *Response: Apologies, this has been modified to reflect non-directive
36 counselling. The 'only sensible option' was a comment on family perception
37 but this has been modified more accurately.*

38
39 *I hope the above modifications meet your approval.*

40
41 *Thank you.*

42
43 *Yours sincerely,*

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51 *Meena Balasubramanian*

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3 **Diagnostic conundrums in antenatal presentation of a skeletal dysplasia with**
4 **description of a heterozygous C-propeptide mutation in *COL1A1* associated with a**
5 **severe presentation of osteogenesis imperfecta**
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10 **Running Title:** *COL1A1* cleavage mutation causing OI

11
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13 C⁵; Bishop, Nicholas J^{2,3}; Balasubramanian, Meena^{2,6}
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53 **Keywords:** C-propeptide cleavage site, *COL1A1*, osteogenesis imperfecta, antenatal
54 presentation, lethal skeletal dysplasia
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ABSTRACT

Prompt and accurate diagnosis of skeletal dysplasias can play a crucial role in ensuring appropriate counseling and management (both antenatal and postnatal). When a skeletal dysplasia is detected during the antenatal period, especially early in the pregnancy, it can be associated with a poor prognosis. It is important to make a diagnosis in antenatal presentation of skeletal dysplasias to inform diagnosis, predict prognosis, provide accurate recurrence risks and options for prenatal genetic testing in future pregnancies.

Prenatal ultrasound scanning is a useful tool to detect several skeletal dysplasias and sonographic measurements serve as reliable indicators of lethality. The lethality depends on various factors including gestational age at which features are identified, size of the chest and progression of malformations. Although, it is important to type the skeletal presentation as accurately as possible, this is not always possible in an antenatal presentation and it is important to acknowledge this uncertainty. In the case of a live birth, it is always important to reassess the infant.

Osteogenesis imperfecta (OI) is a heterogeneous group of disorders characterised by fragile bones. Here, we report an infant with severe OI born following a twin pregnancy in whom the bone disease is caused by a heterozygous pathogenic mutation, c.4160C >T, p.(Ala1387Val) located in the C-propeptide region of *COL1A1*. An assumption of lethality antenatally complicated his management in early life.

We discuss this patient with particular emphasis on the neonatal presentation of a severe skeletal dysplasia and the lessons that may be learned in such situations.

INTRODUCTION

When antenatal imaging identifies short long bones at the 20-week anomaly scan or immediately thereafter, it is important to distinguish a skeletal dysplasia that would not be

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3 compatible with life (such as thanatophoric dysplasia) from a form of skeletal dysplasia that
4 can be treated postnatally to improve outcome (such as osteogenesis imperfecta). This is
5 particularly important as novel therapeutic options are becoming increasingly available to
6 improve outcomes in what were previously thought to be lethal skeletal dysplasias (another
7 recent example is improved outcomes with treatment of hypophosphatasia with asfotase
8 alfa). However, in clinical practice, this is not always straight-forward due to the complexities
9 of clinical management, expertise of professionals involved and difficulties in drawing firm
10 conclusions from antenatal imaging. Also, discussions should involve proposed quality of life
11 rather than survival alone, which is not always possible in these situations. In this case
12 report, we illustrate an example of how such an antenatal presentation of what was thought
13 to be a lethal skeletal dysplasia was subsequently diagnosed as a severe form of OI. With
14 bisphosphonate treatment, combined with regular multidisciplinary review including
15 physiotherapy, this 6-year old boy now has a reasonable quality of life, demonstrating the
16 need for an accurate and precise diagnosis as promptly as possible.
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32 Osteogenesis imperfecta (OI) is the most common form of inherited bone fragility,
33 characterised by fractures and extra-skeletal features including hearing loss, dentinogenesis
34 imperfecta, joint hypermobility and skin hyperextensibility [Lindahl *et al.*, 2015], and is
35 clinically classified into several sub-types [Van Dijk and Sillence, 2014].
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41 Antenatally presenting lethal forms of OI were sub-classified as OI type II and
42 Sillence *et al.*, in 1984 sub-classified this further into 3 categories based on their radiological
43 features: OI type IIA (with short, broad, 'crumpled' long bones, angulation of tibias and
44 continuously beaded ribs); OI type IIB (with short, broad, crumpled femurs, angulation of
45 tibias but normal ribs); and OI type IIC (with long, thin, inadequately modelled long bones,
46 multiple fractures and thin beaded ribs). However, more recent evidence particularly with
47 increased access to genetic analyses suggests that it is unnecessary to sub-classify OI type
48 II as they are indistinguishable clinically with a lot of overlap and some antenatal
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3 presentations have in fact been severe type III OI [Bonafe et al., 2015]. These patients may
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5 survive beyond the perinatal period [Cole et al., 1990].
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8 Here, we present a six year old male patient with a severe, antenatal presentation of
9
10 OI due to a pathogenic mutation in the C-propeptide region of type 1 procollagen and
11
12 discuss his clinical and radiological phenotype in further detail.
13

14 15 16 17 **CLINICAL REPORT**

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19 The proband is a 6-year old boy who was the second to be delivered of dizygotic
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21 twins born at 37 weeks gestation. The parents are non-consanguineous and healthy; his
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23 older half-sister had a history of fracture after insignificant trauma. His twin had no medical
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25 problems. Short long bones were identified on his 20-week anomaly scan and the pregnancy
26
27 was closely monitored. Subsequent scans showed persistent short long bones,
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29 compressible vault and multiple fractures whilst the other twin was reported to be entirely
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31 normal. The family were counseled that the proband was likely to suffer from a lethal skeletal
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33 dysplasia.
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36 He was born with multiple rib and long bone fractures (Figure 1a and b). At birth, he
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38 weighed 2440g and did not require resuscitation. As he was initially thought to have a lethal
39
40 skeletal dysplasia, he remained in the post-natal ward until 3 days of age and subsequently,
41
42 referred for palliative care. He was admitted to a hospice where he received analgesia and
43
44 was fed for comfort. At 11 days of age, he was re-assessed and referred to a specialist
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46 service for children's bone disease. On examination, he was thin and pale, had blue sclerae,
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48 a large anterior fontanelle and normal facies. There was deformity of multiple long bones
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50 with bilateral femoral bowing most noticeable. There was tachypnoea and increased
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52 respiratory effort with a requirement for oxygen to maintain normal transcutaneous oxygen
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54 saturations.
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3 Assessment by the specialist team led to a reconsideration of the approach to his
4 care. He was admitted to hospital and managed according to a standard protocol for infants
5 with OI. He was initially admitted to a high-dependency unit for administration of his first
6 cycle of bisphosphonate treatment (pamidronate 0.5mg/kg x2) and after only a few days was
7 able to be transferred to a paediatric ward. He was found to have a patent foramen ovale at
8 one month of age but this resolved spontaneously. Feeding was complicated by gastro-
9 oesophageal reflux disease for which he was started on hydrolyzed milk feeds. Cranial
10 ultrasonography in the neonatal period did not reveal any abnormality. There was acute
11 deterioration at 5 weeks of age due to bronchiolitis which necessitated a brief period on
12 continuous positive airways pressure. Nonetheless, oxygen dependency persisted until 16
13 months of age.
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26 He received regular cycles of pamidronate according to standard local protocols
27 (12mg/kg/year) with regular assessment by a specialist multidisciplinary team. Gross motor
28 milestones were delayed as one would expect in a child with severe OI. He rolled from front
29 to back at 18 months and was able to sit independently from around 30 months. At 4 years
30 of age, he was crawling on elbows and knees. Multiple surgeries have been undertaken in
31 order to straighten and strengthen his long bones.
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39 At six years of age, his weight was 11.9kg (<2nd centile) and his DXA scan showed
40 areal BMD Z-score at L2-4 of -2.2. Regular monitoring with radiographs and DXA show that,
41 despite bisphosphonate treatment, he has multiple vertebral fractures and a low bone
42 mineral density for his age. He has Erlenmeyer flask deformity of his long bones; a feature
43 seen in some children with OI treated with bisphosphonates. Phenotypically, his clinical
44 features were suggestive of a severe type III OI (Figure 2a and b).
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52 Multiple fractures have limited his progress with walking and he is presently
53 independently mobile in a wheelchair. He receives education alongside his peers in
54 mainstream education with one-to-one help. He has normal speech and normal intelligence.
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57 He has a reasonable quality of life being mobile in a wheel-chair and playful with good social
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3 skills. The course of events associated with the pregnancy and early life have had a
4
5 profound effect on the family. Although he has made good progress in terms of
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7 independence and function, his general quality of life has latterly been affected by frequent
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9 fractures and surgery, both in terms of fear and time spent at hospital.
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11 12 13 14 **METHODS**

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16
17 Genomic DNA was extracted using standard protocols. Clonal sequencing using
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19 SureSelect target enrichment (Agilent Technologies) and the Illumina MiSeq platform was
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21 performed using a custom designed gene panel: *COL1A1*; *COL1A2*; *IFITM5*; *CRTAP*;
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23 *LEPRE1*; *PPIB*; *FKBP10*; *SP7*; *SERPINF1*; *SERPINH1*; *PLOD2*; *BMP1*; *TMEM38B*; *WNT1*.
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25 Analysis of sequence data using a bioinformatics pipeline based on the open source
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27 workflow by the Broad Institute (<http://www.broadinstitute.org/gatk/guide/best-practices>) was
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29 undertaken using a minimum threshold of 30-fold read depth for exonic sequence and
30
31 intron/exon boundary. Sequence variants identified were assessed using the Association for
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33 Clinical Genetic Science Best Practice Guidelines for the evaluation of pathogenicity and the
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35 reporting of sequence variants in clinical molecular genetics (<http://www.acgs.uk.com>).
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41 **RESULTS**

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43 The patient was shown to be heterozygous for a pathogenic *de novo* mutation,
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45 c.4160C > T,p.(Ala1387Val) located in the C-propeptide region of *COL1A1*. This particular
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47 mutation had been reported in one family with a recurrence of severe OI [Takagi et al.,
48
49 2011]. He was also found to be heterozygous for a novel c.3278G > A, p.(Arg1093His)
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51 variant in the helical domain of *COL1A1*. This variant was found in the mother who showed
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53 no features of OI and hence, is most likely a benign polymorphism.
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DISCUSSION

The most common mutations causing OI (accounting for around 90% of cases) are found in the *COL1A1* and *COL1A2* genes, encoding the $\alpha 1$ and $\alpha 2$ chains of collagen type I respectively. Each α chain contains a triple helical region flanked by N and C-propeptide domains at the amino- and carboxyl-terminal ends, which are cleaved at the final assembly of the type I collagen heterotrimer [Takagi *et al.*, 2014]. Current literature describes the most common mutations causing OI to be glycine substitutions in the triple helical domain which breaks the repetitive (Gly-X-Y)_n pattern of either *COL1A1* or *COL1A2*. These can be associated with a range of phenotypes, from mild to severe, dependent on how protein folding and structure are affected [Lindahl *et al.*, 2015].

The phenotypic outcome of C-propeptide mutations is highly variable. Mutations resulting in a premature termination codon differ depending on their location: mild OI phenotypes can be caused by nonsense mutations 50-55 nucleotides upstream of the 3' exon-exon junction whereas those that lie beyond this, or within the last exon, are more usually associated with severe to lethal OI as they escape nonsense mediated mRNA decay, meaning stable, overmodified procollagen chains are formed [Symoens *et al.*, 2014]. However in our proband, a missense mutation in *COL1A1* was observed. With missense mutations, phenotypes differ depending on the location within the C-propeptide region and type of substitution. Review of published literature on C-propeptide missense mutations suggests that a patient with a mutation in exon 52 of *COL1A1* c.4321G>T, p.(Asp1441Tyr) had a lethal form of OI with features of dense bone disease; [Pace *et al.*, 2002]. However, Lu *et al.*, 2014 described two patients with C-propeptide missense mutations: the first was c.3835A>C, p.(Asn1279His) resulting in OI type III (intrauterine rib and clavicle fractures; unable to walk due to leg deformities); the second was c.3893C>A, p.(Thr1298Asn) resulting in OI type IV (recurrent femoral fractures with pseudoarthritis).

Other phenotypes resulting from a C-propeptide variant of *COL1A1* include OI with dense bone disease- see below [Takagi *et al.*, 2011] and gnathodiaphyseal dysplasia, which

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2
3 has previously been described as OI with 'unusual skeletal features' [McInerney-Leo *et al.*,
4 2014]. Hence, there can be consistent phenotypic correlation for some OI-causing variants,
5 such as for the *COL1A1* c.4237G>A; p.(Asp1413Asn) described in type II OI, but a lack of
6 phenotypic correlation for others.
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10
11 Takagi *et al.*, 2011 reported two siblings with the same mutation as our proband. In
12 this case report, the mutation in C-propeptide region of *COL1A1* resulted in a severe OI that
13 was assumed to be lethal on the basis of antenatal scans and postnatal radiographs. In this
14 report, Patient 2-1 had bowed limbs and a hypoplastic thorax on fetal ultrasound; she was
15 delivered at 37 weeks and died at 4 months of age. However, there were few details about
16 this infant and, although she is described as requiring ventilatory support, the exact details
17 surrounding her death are unclear. It is to be presumed that she did not receive treatment
18 with bisphosphonates. In contrast, her younger brother, Patient 2-2 was born at 37 weeks
19 with multiple long bone and rib fractures. He required long term respiratory support, was
20 started on pamidronate at 11 months and was still alive at 11 years. He has never sat
21 without support but the reason for this and the level of specialist therapy intervention is
22 unclear. Although he had a more severe course, this second patient's presentation is similar
23 to our patient and the presenting radiographic appearances are similar.
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39 Antenatal presentation of a skeletal dysplasia is usually in the form of short, long
40 bones (micromelia) identified at the 20-week anomaly scan but may present with additional
41 features such as bowing of the long bones, small chest, under-mineralised bones and
42 fractures. Useful pointers to aid diagnosis on antenatal imaging are chest circumference;
43 size, shape and degree of mineralisation of long bones; any evidence of angulation/
44 fractures; appearance of vertebral bodies; hands (trident hand/ polydactyly); evidence of
45 frontal bossing, micrognathia. Indicators to predict lethality include chest size, limb length
46 and specific to OI, include angulation of tibiae/fibulae, multiplicity of fractures. Most lethal
47 forms of skeletal dysplasias are diagnosed in the first or second trimester of pregnancy.
48 There are many differential diagnoses in this situation (common examples being
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3 achondrogenesis (types 1a, 1b and 2), thanatophoric dysplasia, lethal OI, perinatal
4 hypophosphatasia, short rib dysplasias). It is important to consult specialists from various
5 disciplines particularly Genetics (to obtain extended family history, check if clinical features
6 are compatible with a specific diagnosis and direct specific gene testing where appropriate,
7 especially as targeted skeletal gene panels become increasingly available), Neonatology (to
8 ensure appropriate early management which has an implication on outcomes), Radiologists
9 (to provide an opinion as to the precise skeletal dysplasia) and specialists in management of
10 the specific condition where identified. This is becoming increasingly relevant as therapies
11 are available to improve outcomes in this rare disease group which makes a difference
12 between life and death in these children. Examples include treatment with bisphosphonates
13 in OI, asfotase alfa in perinatal/ infantile hypophosphatasia. Ultimately, survival in this group
14 will depend on respiratory capacity and the nature of the underlying condition. However,
15 having a combined, stratified approach would ensure the best chance of survival in these
16 children, increased rate of precise diagnoses and accurate sibling recurrence risks for
17 families in this situation. As is evident from our patient, this potentially has a huge impact on
18 survival and postnatal outcome.

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36 However, obtaining a precise diagnosis is not always possible in an antenatal
37 presentation of a potentially lethal skeletal dysplasia and confirmatory genetic testing is only
38 partially helpful as results may take several weeks, does not always provide accurate
39 prognostic information and/ or aid in predicting mortality. It is important that parents are
40 counseled with all available information (or lack of) including discussions on quality of life in
41 order for them to make an informed decision. In our experience, families who have been
42 provided with a diagnosis of severe OI antenatally often report having been presented with a
43 pessimistic view of long term outcomes and quality of life, and recall the impression that
44 termination of pregnancy was advanced as the only reasonable choice. Whilst antenatal
45 assessment is crucial in providing families with advice, it is essential that this is undertaken
46 in a non-directive manner. Limitations in diagnostic and prognostic accuracy need to be
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3 understood with consideration given to involvement of specialist paediatric teams in the
4 antenatal decision-making processes, as deemed appropriate. Certainly, infants who survive
5 the period immediately following birth should be assessed by or an opinion sought from an
6 appropriately skilled clinician. It is also important that clinicians guard against assuming that
7 an antenatal diagnosis is correct, lest the assertion that the condition is lethal becomes a
8 self-fulfilling prophesy either through a delay or withholding of care. Clearly children with OI
9 do well with a reasonable quality of life when the diagnosis is made early and treatment with
10 multi-disciplinary input instituted immediately after birth. This has resulted in marked
11 improvement in quality of life for these patients and their families who question the
12 information given to them in the antenatal period (as in this patient).
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24 Our case adds to the growing evidence of literature on mutations in the C-propeptide
25 region being associated with a severe OI phenotype. This needs to be considered in the
26 differential diagnoses of a lethal skeletal dysplasia especially when presenting antenatally
27 with fractures.
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35 **ACKNOWLEDGEMENTS**

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37 We thank this family for their participation in this report.
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3 Figure 1a and b: Radiographs at day 1 demonstrating 1a: AP Chest (aged 1 day): Multiple
4 acute and healing ribs, humeral and clavicular fractures. Although the bones are slender,
5 there is normal bone density. Note preservation of vertebral body height.
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10 1b: AP Left Leg (aged 1 day): Fractured long bones. The angulation of the tibia and fibula is
11 characteristically seen in perinatally lethal OI.
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14 Figure 2a and b: Imaging at 4.5 years of age demonstrating the face and significant limb
15 deformities in our proband.
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For Peer Review

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Fig 2a

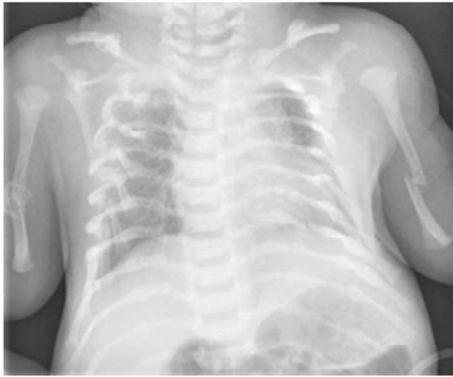


Fig 2b



Figure 1a and b: Radiographs at day 1 demonstrating 1a: AP Chest (aged 1 day): Multiple acute and healing ribs, humeral and clavicular fractures. Although the bones are slender, there is normal bone density. Note preservation of vertebral body height.
1b: AP Left Leg (aged 1 day): Fractured long bones. The angulation of the tibia and fibula is characteristically seen in perinatally lethal OI.

Figure 1
279x209mm (96 x 96 DPI)

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Fig 1a



Fig 1b



Figure 2a and b: Imaging demonstrating the face and significant limb deformities in our proband.

Figure 2

279x209mm (96 x 96 DPI)

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