This is a repository copy of *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*.

White Rose Research Online URL for this paper:
http://eprints.whiterose.ac.uk/105140/

Version: Accepted Version

Article:
Marshall, C.J., Arundel, P., Mushtaq, T. et al. (4 more authors) (2016) 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. American Journal of Medical Genetics Part A, 170 (12). pp. 3303-3307. ISSN 1552-4825

https://doi.org/10.1002/ajmg.a.37943

Reuse
Unless indicated otherwise, fulltext items are protected by copyright with all rights reserved. The copyright exception in section 29 of the Copyright, Designs and Patents Act 1988 allows the making of a single copy solely for the purpose of non-commercial research or private study within the limits of fair dealing. The publisher or other rights-holder may allow further reproduction and re-use of this version - refer to the White Rose Research Online record for this item. Where records identify the publisher as the copyright holder, users can verify any specific terms of use on the publisher's website.

Takedown
If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

eprints@whiterose.ac.uk
https://eprints.whiterose.ac.uk/

American Journal of Medical Genetics Part A

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

Journal:	*American Journal of Medical Genetics: Part A*
Manuscript ID	16-0094.R2
Wiley - Manuscript type:	Clinical Report
Date Submitted by the Author:	n/a
Keywords:	COL1A1, Osteogenesis Imperfecta, high bone mass phenotype, C-propeptide cleavage site
Search Terms:	Osteogenesis Imperfecta, Bone fragility, Bone mass, COL1A1

Complete List of Authors:
Marshall, Charlotte; University of Sheffield Medical School
Arundel, Paul; University of Sheffield, Academic Unit of Child Health
Mushtaq, Talat; Leeds Teaching Hospitals NHS Trust, Department of Paediatric Endocrinology
Offiah, Amaka; Sheffield Children's NHS Foundation Trust, Academic Unit of Child Health
Pollitt, Rebecca; Sheffield Children's NHS Foundation Trust, Sheffield Diagnostic Genetics Department
Bishop, Nick; Sheffield Children's Hospital, Department of Paediatric Bone Disease
Balasubramanian, Meena; Sheffield Children's NHS Foundation Trust, Sheffield Clinical Genetics Service;

SCHOLARONE™
Manuscripts

Subject: AJMG - MS 16-0094 Revision Required

Dear Prof Hennekam,

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

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

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

Sincerely,

Meena Balasubramanian
Consultant in Clinical Genetics
Lead Consultant, OI-Genetics Service, Highly Specialised Severe, Complex & Atypical OI Service
Honorary Senior Clinical Lecturer, Dept. of Human Metabolism, University of Sheffield
Sheffield Clinical Genetics Service
Sheffield Children's NHS Foundation Trust
Western Bank, Sheffield S10 2TH

Title: A Heterozygous C-propeptide Mutation in COL1A1 Associated with a Severe, Antenatal Presentation of Osteogenesis Imperfecta

Response to Editor's Comments:

Your manuscript has been evaluated by one of the Original reviewers who was in general pleased with the way you have adapted the manuscript. I concur. The reviewer still has a few remarks, which do need attention. In addition I noticed that some of the references are incomplete, and none of the references have used the international abbreviations of the journal's names (as can be found in PubMed). Please check the guidelines for authors on the site and.

Response: Sincere apologies for this, corrected references in manuscript according to author instructions.

Please resubmit the manuscript with a rebuttal letter mentioning all issues raised by reviewer and editor, and how you have incorporated these into the manuscript. I will re-evaluate the manuscript thereafter myself. If adequately

For Peer Review

changed I shall then be pleased to advise the Editor-in-Chief to accept the manuscript.

Response: Thank you.

Response to Reviewer Comments:

Reviewer: 1

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

Response: Thank you.

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

Response: Apologies, corrected.

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

Response: Apologies, corrected.

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

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

I hope the above modifications meet your approval.

Thank you.

Yours sincerely,

Meena Balasubramanian

For Peer Review

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

Running Title: *COL1A1* cleavage mutation causing OI

Marshall, Charlotte[1]; Arundel, Paul[2,3]; Mushtaq, Talat[4]; Offiah, Amaka C[2,3]; Pollitt, Rebecca C[5]; Bishop, Nicholas J[2,3], Balasubramanian, Meena[2,6]

[1]Medical School, University of Sheffield, UK

[2]Highly Specialised Service for Severe, Complex and Atypical OI Service, Sheffield Children's NHS Foundation Trust, Sheffield, UK

[3]Academic Unit of Child Health, University of Sheffield, UK

[4]Department of Paediatric Endocrinology, Leeds Teaching Hospitals, UK

[5]Sheffield Diagnostic Genetics Service, Sheffield Children's NHS Foundation Trust, UK

[6]Sheffield Clinical Genetics Service, Sheffield Children's NHS Foundation Trust, UK

Correspondence to:

Dr Meena Balasubramanian

Sheffield Clinical Genetics Service

Sheffield Children's NHS Foundation Trust

Western Bank, Sheffield S10 2TH

Ph- +44 114 2717025

Fax- +44 114 2737467

E-mail-meena.balasubramanian@nhs.net

Keywords: C-propeptide cleavage site, *COL1A1*, osteogenesis imperfecta, antenatal presentation, lethal skeletal dysplasia

For Peer Review

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

For Peer Review

compatible with life (such as thanatophoric dysplasia) from a form of skeletal dysplasia that can be treated postnatally to improve outcome (such as osteogenesis imperfecta). This is particularly important as novel therapeutic options are becoming increasingly available to improve outcomes in what were previously thought to be lethal skeletal dysplasias (another recent example is improved outcomes with treatment of hypophosphatasia with asfotase alfa). However, in clinical practice, this is not always straight-forward due to the complexities of clinical management, expertise of professionals involved and difficulties in drawing firm conclusions from antenatal imaging. Also, discussions should involve proposed quality of life rather than survival alone, which is not always possible in these situations. In this case report, we illustrate an example of how such an antenatal presentation of what was thought to be a lethal skeletal dysplasia was subsequently diagnosed as a severe form of OI. With bisphosphonate treatment, combined with regular multidisciplinary review including physiotherapy, this 6-year old boy now has a reasonable quality of life, demonstrating the need for an accurate and precise diagnosis as promptly as possible.

Osteogenesis imperfecta (OI) is the most common form of inherited bone fragility, characterised by fractures and extra-skeletal features including hearing loss, dentinogenesis imperfecta, joint hypermobility and skin hyperextensibility [Lindahl et al., 2015], and is clinically classified into several sub-types [Van Dijk and Sillence, 2014].

Antenatally presenting lethal forms of OI were sub-classified as OI type II and Sillence et al., in 1984 sub-classified this further into 3 categories based on their radiological features: OI type IIA (with short, broad, 'crumpled' long bones, angulation of tibias and continuously beaded ribs); OI type IIB (with short, broad, crumpled femurs, angulation of tibias but normal ribs); and OI type IIC (with long, thin, inadequately modelled long bones, multiple fractures and thin beaded ribs). However, more recent evidence particularly with increased access to genetic analyses suggests that it is unnecessary to sub-classify OI type II as they are indistinguishable clinically with a lot of overlap and some antenatal

For Peer Review

presentations have in fact been severe type III OI [Bonafe et al., 2015]. These patients may survive beyond the perinatal period [Cole et al., 1990].

Here, we present a six year old male patient with a severe, antenatal presentation of OI due to a pathogenic mutation in the C-propeptide region of type 1 procollagen and discuss his clinical and radiological phenotype in further detail.

CLINICAL REPORT

The proband is a 6-year old boy who was the second to be delivered of dizygotic twins born at 37 weeks gestation. The parents are non-consanguineous and healthy; his older half-sister had a history of fracture after insignificant trauma. His twin had no medical problems. Short long bones were identified on his 20-week anomaly scan and the pregnancy was closely monitored. Subsequent scans showed persistent short long bones, compressible vault and multiple fractures whilst the other twin was reported to be entirely normal. The family were counseled that the proband was likely to suffer from a lethal skeletal dysplasia.

He was born with multiple rib and long bone fractures (Figure 1a and b). At birth, he weighed 2440g and did not require resuscitation. As he was initially thought to have a lethal skeletal dysplasia, he remained in the post-natal ward until 3 days of age and subsequently, referred for palliative care. He was admitted to a hospice where he received analgesia and was fed for comfort. At 11 days of age, he was re-assessed and referred to a specialist service for children's bone disease. On examination, he was thin and pale, had blue sclerae, a large anterior fontanelle and normal facies. There was deformity of multiple long bones with bilateral femoral bowing most noticeable. There was tachypnoea and increased respiratory effort with a requirement for oxygen to maintain normal transcutaneous oxygen saturations.

For Peer Review

Assessment by the specialist team led to a reconsideration of the approach to his care. He was admitted to hospital and managed according to a standard protocol for infants with OI. He was initially admitted to a high-dependency unit for administration of his first cycle of bisphosphonate treatment (pamidronate 0.5mg/kg x2) and after only a few days was able to be transferred to a paediatric ward. He was found to have a patent foramen ovale at one month of age but this resolved spontaneously. Feeding was complicated by gastro-oesophageal reflux disease for which he was started on hydrolyzed milk feeds. Cranial ultrasonography in the neonatal period did not reveal any abnormality. There was acute deterioration at 5 weeks of age due to bronchiolitis which necessitated a brief period on continuous positive airways pressure. Nonetheless, oxygen dependency persisted until 16 months of age.

He received regular cycles of pamidronate according to standard local protocols (12mg/kg/year) with regular assessment by a specialist multidisciplinary team. Gross motor milestones were delayed as one would expect in a child with severe OI. He rolled from front to back at 18 months and was able to sit independently from around 30 months. At 4 years of age, he was crawling on elbows and knees. Multiple surgeries have been undertaken in order to straighten and strengthen his long bones.

At six years of age, his weight was 11.9kg (<2nd centile) and his DXA scan showed areal BMD Z-score at L2-4 of -2.2. Regular monitoring with radiographs and DXA show that, despite bisphosphonate treatment, he has multiple vertebral fractures and a low bone mineral density for his age. He has Erlenmeyer flask deformity of his long bones; a feature seen in some children with OI treated with bisphosphonates. Phenotypically, his clinical features were suggestive of a severe type III OI (Figure 2a and b).

Multiple fractures have limited his progress with walking and he is presently independently mobile in a wheelchair. He receives education alongside his peers in mainstream education with one-to-one help. He has normal speech and normal intelligence. He has a reasonable quality of life being mobile in a wheel-chair and playful with good social

For Peer Review

skills. The course of events associated with the pregnancy and early life have had a profound effect on the family. Although he has made good progress in terms of independence and function, his general quality of life has latterly been affected by frequent fractures and surgery, both in terms of fear and time spent at hospital.

METHODS

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

RESULTS

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

For Peer Review

DISCUSSION

The most common mutations causing OI (accounting for around 90% of cases) are found in the *COL1A1* and *COL1A2* genes, encoding the proα1 and proα2 chains of collagen type I respectively. Each proαchain 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 $(Gly\text{-}X\text{-}Y)_n$ 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

For Peer Review

has previously been described as OI with 'unusual skeletal features' [McInerney-Leo et al., 2014]. Hence, there can be consistent phenotypic correlation for some OI-causing variants, such as for the *COL1A1* c.4237G>A; p.(Asp1413Asn) described in type II OI, but a lack of phenotypic correlation for others.

Takagi et al., 2011 reported two siblings with the same mutation as our proband. In this case report, the mutation in C-propeptide region of *COL1A1* resulted in a severe OI that was assumed to be lethal on the basis of antenatal scans and postnatal radiographs. In this report, Patient 2-1 had bowed limbs and a hypoplastic thorax on fetal ultrasound; she was delivered at 37 weeks and died at 4 months of age. However, there were few details about this infant and, although she is described as requiring ventilatory support, the exact details surrounding her death are unclear. It is to be presumed that she did not receive treatment with bisphosphonates. In contrast, her younger brother, Patient 2-2 was born at 37 weeks with multiple long bone and rib fractures. He required long term respiratory support, was started on pamidronate at 11 months and was still alive at 11 years. He has never sat without support but the reason for this and the level of specialist therapy intervention is unclear. Although he had a more severe course, this second patient's presentation is similar to our patient and the presenting radiographic appearances are similar.

Antenatal presentation of a skeletal dysplasia is usually in the form of short, long bones (micromelia) identified at the 20-week anomaly scan but may present with additional features such as bowing of the long bones, small chest, under-mineralised bones and fractures. Useful pointers to aid diagnosis on antenatal imaging are chest circumference; size, shape and degree of mineralisation of long bones; any evidence of angulation/ fractures; appearance of vertebral bodies; hands (trident hand/ polydactyly); evidence of frontal bossing, micrognathia. Indicators to predict lethality include chest size, limb length and specific to OI, include angulation of tibiae/fibulae, multiplicity of fractures. Most lethal forms of skeletal dysplasias are diagnosed in the first or second trimester of pregnancy. There are many differential diagnoses in this situation (common examples being

For Peer Review

achondrogenesis (types 1a, 1b and 2), thanatophoric dysplasia, lethal OI, perinatal hypophosphatasia, short rib dysplasias). It is important to consult specialists from various disciplines particularly Genetics (to obtain extended family history, check if clinical features are compatible with a specific diagnosis and direct specific gene testing where appropriate, especially as targeted skeletal gene panels become increasingly available), Neonatology (to ensure appropriate early management which has an implication on outcomes), Radiologists (to provide an opinion as to the precise skeletal dysplasia) and specialists in management of the specific condition where identified. This is becoming increasingly relevant as therapies are available to improve outcomes in this rare disease group which makes a difference between life and death in these children. Examples include treatment with bisphosphonates in OI, asfotase alfa in perinatal/ infantile hypophosphatasia. Ultimately, survival in this group will depend on respiratory capacity and the nature of the underlying condition. However, having a combined, stratified approach would ensure the best chance of survival in these children, increased rate of precise diagnoses and accurate sibling recurrence risks for families in this situation. As is evident from our patient, this potentially has a huge impact on survival and postnatal outcome.

However, obtaining a precise diagnosis is not always possible in an antenatal presentation of a potentially lethal skeletal dysplasia and confirmatory genetic testing is only partially helpful as results may take several weeks, does not always provide accurate prognostic information and/ or aid in predicting mortality. It is important that parents are counseled with all available information (or lack of) including discussions on quality of life in order for them to make an informed decision. In our experience, families who have been provided with a diagnosis of severe OI antenatally often report having been presented with a pessimistic view of long term outcomes and quality of life, and recall the impression that termination of pregnancy was advanced as the only reasonable choice. Whilst antenatal assessment is crucial in providing families with advice, it is essential that this is undertaken in a non-directive manner. Limitations in diagnostic and prognostic accuracy need to be

For Peer Review

understood with consideration given to involvement of specialist paediatric teams in the antenatal decision-making processes, as deemed appropriate. Certainly, infants who survive the period immediately following birth should be assessed by or an opinion sought from an appropriately skilled clinician. It is also important that clinicians guard against assuming that an antenatal diagnosis is correct, lest the assertion that the condition is lethal becomes a self-fulfilling prophesy either through a delay or withholding of care. Clearly children with OI do well with a reasonable quality of life when the diagnosis is made early and treatment with multi-disciplinary input instituted immediately after birth. This has resulted in marked improvement in quality of life for these patients and their families who question the information given to them in the antenatal period (as in this patient).

Our case adds to the growing evidence of literature on mutations in the C-propeptide region being associated with a severe OI phenotype. This needs to be considered in the differential diagnoses of a lethal skeletal dysplasia especially when presenting antenatally with fractures.

For Peer Review

ACKNOWLEDGEMENTS

We thank this family for their participation in this report.

REFERENCES

Bonafe L, Cormier-Daire V, Hall C, Lachman R, Mortier G, Mundlos S, Nishimura G, Sangiorgi L, Savarirayan R, Sillence D. 2015. Nosology and classification of genetic skeletal disorders: 2015 revision. Am J Med Genet A 167A(12):2869-92

Cole W, Campbell P, Rogers J, Bateman J. 1990. The clinical features of osteogenesis imperfecta resulting from a non-functional carboxy terminal pro alpha 1 (I) propeptide of type

I procollagen and a severe deficiency of normal type I collagen in tissues. J Med Genet 27(9):545-551.

Lindahl K, Barnes AM, Fratzl-Zelman N, Whyte MP, Hefferan TE, Makareeva E, Brusel M, Yaszemski MJ, Rubin CJ, Kindmark A. 2011. COL1 C-propeptide cleavage site mutations cause high bone mass osteogenesis imperfecta. Hum Mut 32(6):598-609.

Lindahl K, Åström E, Rubin C-J, Grigelioniene G, Malmgren B, Ljunggren Ö, Kindmark A. 2015. Genetic epidemiology, prevalence, and genotype–phenotype correlations in the Swedish population with osteogenesis imperfecta. Eur J Hum Genet 23(8):1042-50.

McInerney-Leo A, Duncan E, Leo P, Gardiner B, Bradbury L, Harris J, Clark G, Brown M, Zankl A. 2015. COL1A1 C-propeptide cleavage site mutation causes high bone mass, bone fragility and jaw lesions: a new cause of gnathodiaphyseal dysplasia? Clin Genet 88(1):49-55.

Pace J, Chitayat D, Atkinson M, Wilcox W, Schwarze U, Byers P. 2002. A single amino acid substitution (D1441Y) in the carboxyl-terminal propeptide of the proα1 (I) chain of type I collagen results in a lethal variant of osteogenesis imperfecta with features of dense bone diseases. J Med Genet 39(1):23-29.

Symoens S, Hulmes DJ, Bourhis JM, Coucke PJ, De Paepe A, Malfait F. 2014. Type I procollagen C-Propeptide defects: Study of genotype–phenotype correlation and predictive role of crystal structure. Hum Mut 35(11):1330-1341.

Takagi M, Hori N, Chinen Y, Kurosawa K, Tanaka Y, Oku K, Sakata H, Fukuzawa R, Nishimura G, Spranger J. 2011. Heterozygous C-propeptide mutations in COL1A1: Osteogenesis imperfecta type IIC and dense bone variant. Am J Med Genet Part A 155(9):2269-2273.

Van Dijk F, Sillence D. 2014. Osteogenesis imperfecta: clinical diagnosis, nomenclature and severity assessment. Am J Med Genet Part A 164(6):1470-1481.

FIGURE LEGENDS

For Peer Review

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 2a and b: Imaging at 4.5 years of age demonstrating the face and significant limb deformities in our proband.

For Peer Review

Fig 2a

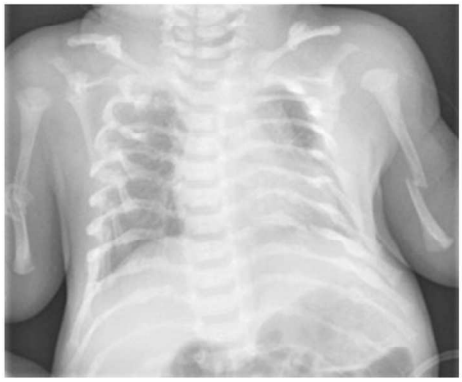

Fig 2b

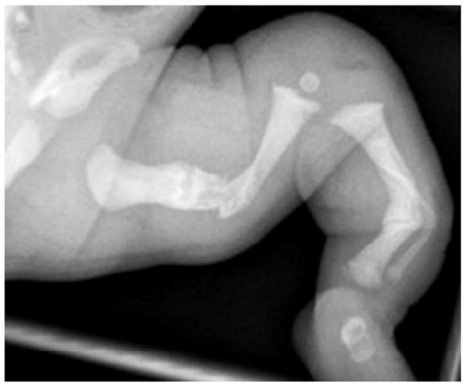

Figure 1a and b: Radiographs at day 1 demonstrating 1a: AP Chest (aged 1 day): Multiple acute and healing ribs, humeral and clavicular fractures. Although the bones are slender, there is normal bone density. Note preservation of vertebral body height.
1b: AP Left Leg (aged 1 day): Fractured long bones. The angulation of the tibia and fibula is characteristically seen in perinatally lethal OI.
Figure 1
279x209mm (96 x 96 DPI)

iew

Fig 1a Fig Ib

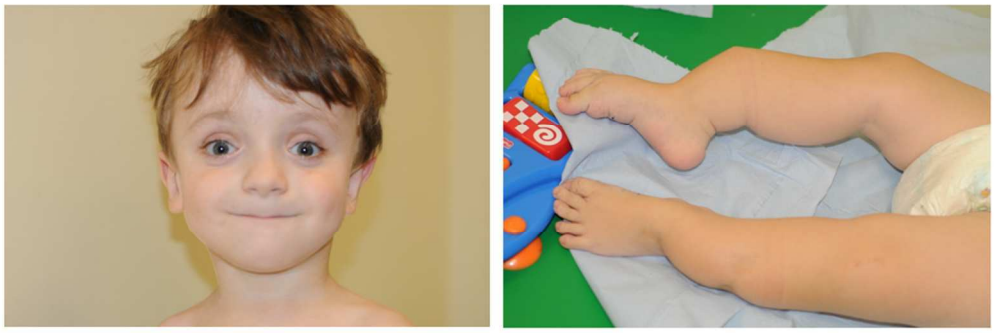

Figure 2a and b: Imaging demonstrating the face and significant limb deformities in our proband.
Figure 2
279x209mm (96 x 96 DPI)

For Review