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A Novel Dominant *COL11A1* Mutation Resulting in a Severe Skeletal Dysplasia

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Abstract

Mutations in the type XI collagen alpha-1 chain gene (*COL11A1*) cause a change in protein structure that alters its interactions with collagens II and V, resulting in abnormalities in cartilage and ocular vitreous. The most common type XI collagenopathies are dominantly inherited Stickler or Marshall syndromes, while severe recessive skeletal dysplasias, such as fibrochondrogenesis, occur less frequently. We describe a family with a severe skeletal dysplasia caused by a novel dominantly inherited *COL11A1* mutation. The siblings each presented with severe myopia, hearing loss, micromelia, metaphyseal widening of the long bones, micrognathia and airway compromise requiring tracheostomy. The first child lived for over 2 years, while the second succumbed at 5 months of age. Their mother has mild rhizomelic shortening of the limbs, brachydactyly, and severe myopia. Sequencing of *COL11A1* revealed a novel deleterious heterozygous mutation in *COL11A1* involving the triple helical domain in both siblings, and a mosaic mutation in their mother, indicating germline mosaicism with subsequent dominant inheritance. These are the first reported individuals with a dominantly inherited mutation in *COL11A1* associated with a severe skeletal dysplasia. The skeletal involvement is similar to, yet milder than fibrochondrogenesis and allowed for survival beyond the perinatal period. These cases highlight both a novel dominant *COL11A1* mutation causing a significant skeletal dysplasia and the phenotypic heterogeneity of collagenopathies.

Keywords

fibrochondrogenesis; skeletal dysplasia; *COL11A1* ; collagen; cartilage

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ONLINE RESOURCES
Online Mendelian Inheritance in Man (MIM): http://www.ncbi.nlm.nih.gov/Omim.
SMART Protein model: http://smart.embl-heidelberg.de/
PROVEAN analysis: http://provean.jcvi.org/seq_submit.php

INTRODUCTION

The collagenopathies are a diverse group of heritable disorders in which defects in structural collagen lead to a wide range of skeletal and eye anomalies [Spranger, 1998; Winter et al., 1983]. There are over 450 distinct skeletal dysplasias many of which are caused by disruptions in development of cartilage, which lead to abnormalities in the eye and musculoskeletal system [Warman et al., 2011]. The incidence of skeletal dysplasia is estimated to be 4 in every 10,000 live births, with phenotypic severity varying from mild to perinatal lethal [Carter and Raggio, 2009]. The diagnosis may be suspected prenatally based on imaging. Specific diagnosis often requires postnatal clinical, radiographic, and molecular evaluation. Treatment is dependent on the specific diagnosis and severity of symptoms, often requiring supportive multi-disciplinary care.

Collagens are fibrous structural proteins involved in the construction of skin, cartilage, bone, eye, and many other tissues [Carter and Raggio, 2009; Spranger, 1998]. They are composed of a right-handed triple helix with three polypeptide alpha chains. The chains are comprised of repetitive triplet amino acids, glycine-X-Y, in which “X” and “Y” can be any amino acid. In the rough endoplasmic reticulum (RER), the helices of three different alpha chains wrap into each other, creating a fibrous rope-like protein. Depending on the tissue involved, the size and shape of the structure varies [Carter and Raggio, 2009]. The triple helical structure is critical for collagen stability. It has been proposed that disruption of the triple helical structure leads to abnormal folding of the collagen proteins, and a detrimental clinical phenotype [Carter and Raggio, 2009].

Twenty-nine different collagen proteins have been identified to date, comprised of products from more than 40 genes [Carter and Raggio, 2009; Spranger, 1998]. The interactions between collagen types play a crucial role in the development and proliferation of cartilaginous and non-cartilaginous tissues. For example, collagen subgroup types XI and V interact with types I, II, and III to create the fibrillar lattice found in cartilage. Furthermore, collagen XI interacts with collagens II and V, forming a heterotrimer supporting many non-cartilaginous tissues, such as the ocular vitreous [Alzahrani et al., 2012; Richards et al., 2010].

The type XI procollagen structure is composed of three alpha chain products from the following genes: *COL11A1, COL11A2*, and *COL2A1*. The *COL11A1* gene (OMIM: 120280) encodes the alpha-1 chain of type XI collagen. Missense substitution or in-frame deletion mutations in *COL11A1* may result in a dominant negative effect on the synthesis, secretion, assembly, and turnover of collagen [Vuoristo et al., 1996].

Chondrodysplasia (cho) mouse models have irregularities in their cartilage caused by a frameshift mutation leading to premature truncation of the collagen XI alpha chain. Homozygous cho −/− mice are born with a severe skeletal dysplasia, dying soon after birth from pulmonary hypoplasia. In contrast, heterozygous cho +/− mice have a much less severe phenotype, often manifested as shortening of the long bones [Li et al., 1995]. Similar presentations are noted in humans. Specifically, heterozygous mutations in *COL11A1* typically result in milder autosomal dominant phenotype, such as Stickler or

Marshall syndrome, while homozygous and compound heterozygous mutations result in a more severe autosomal recessive skeletal dysplasia, such as fibrochondrogenesis. Mutations in *COL11A1*, however, may lead to a variety of phenotypes. Such phenotypes may lie along the severity spectrum between that of Sticker syndrome, Marshall syndrome, and fibrochondrogenesis while other phenotypes are separate from these diagnoses. We describe siblings with a novel heterozygous mutation in *COL11A1* and a severe skeletal dysplasia as well as their mosaic mother. Insight into the phenotypic spectrum of collagenopathies can be gained by comparing our patients with other described *COL11A1* phenotypes.

CLINICAL REPORT

We present a family with siblings affected by a severe skeletal dysplasia born to a mildly affected mother. Please refer to Figure 1 for the pedigree.

Patient II-1 was a female born at 32 weeks gestation due to premature rupture of membranes. Craniofacial anomalies included frontal bossing, midfacial retrusion, proptosis, glossoptosis, micrognathia, and cleft palate. Extremity exam demonstrated micromelia with rhizomelic shortening, and brachydactyly. Ophthalmologic evaluation revealed high myopia. Sensorineural hearing loss was discovered on audiologic testing. Prenatal suspicion for thanatophoric dysplasia prompted testing analysis of *FGFR3*, which was normal. Postnatal evaluation via radiographic imaging demonstrated short, dumbbell shaped long bones with metaphyseal widening and small scapulae (Fig. 2). Birth weight and head circumference were at the 10th and 50th centile, respectively. However, her height, long bone length, digit length, and chest diameter were each symmetrically below the 3rd centile. There was initially no evidence of pulmonary hypoplasia. However, the infant required a tracheostomy placement, without ventilation, shortly after birth due to upper airway obstruction from micrognathia and glossoptosis. As the patient grew, thoracic insufficiency worsened over the first 2 years of life, inhibiting pulmonary development, resulting in further dependence on her tracheostomy and an eventual ventilation requirement. At 26 months of age, she passed away due to a dislodged tracheostomy.

Patient II-3 was noted on prenatal ultrasound to have micromelia, micrognathia, and cleft palate. Given the similar presentation in her deceased sister, *COL11A1* and *COL2A2* sequencing was performed via amniocentesis. A heterozygous deletion in *COL11A1* involving exon 48, c.3627_3635del9 was identified. This mutation results in the loss of 3 amino acids (p.1209_1211delLys-Gly-Glu) in the triple helical domain of the collagen XI alpha-1 chain.

Delivery was at 40 weeks. She required tracheostomy placement soon after birth due to micrognathia and upper airway obstruction resulting in respiratory compromise. Her physical exam and skeletal findings closely matched that of her sister (Fig. 4). Her birth weight and head circumference were at the 25th and 75th centile, respectively, while her height, long bone length, digit length, and chest diameter were each symmetrically below the 3rd centile. At the age of 5 months, she passed away due to mucous plugging of the tracheostomy.

The mother, Patient I-2, is a 33-year-old intellectually normal Caucasian woman with mildly short limbs with rhizomelia and brachydactyly, high myopia, as well as mild dysmorphic features including a flat nasal bridge, short nose with anteverted nares, bilateral epicanthic folds, shallow orbits, and prominent eyes. Her peripheral blood analysis, obtained after the positive amniocenteses results noted in Patient II-3, revealed 10% mosaicism for the same *COL11A1* mutation.

Family history is otherwise non-contributory. Patient II-1 and II-3 have a sister who is healthy with normal vision and stature. They all have the same father, who is also healthy with normal vision and stature. Medications, drugs, alcohol, infections, and environmental toxins were denied in all pregnancies. There was no consanguinity.

DISCUSSION

In this report, we describe two sisters with a novel deletion in *COL11A1* affecting the triple helical domain of the collagen XI alpha-1 chain, inherited from their mother who had mosaicism for the same mutation. The similar presentations in each daughter, the milder presentation and mosaicism noted in the mother, and the lack of paternal family history are consistent with autosomal dominant inheritance.

Heterozygous *COL11A1* mutations usually present with milder non-lethal phenotypes, such as Stickler or Marshall syndromes, in contrast to those seen in our patients. The most common manifestation is dominantly inherited Stickler syndrome type 2 (OMIM: 604841) [Richards et al., 1996], characterized by myopia, sensorineural or conductive hearing loss, midface retrusion, Robin sequence, mild spondyloepiphyseal dysplasia, and precocious osteoarthritis [Snead et al., 1994; Snead and Yates, 1999; Snead et al., 1996]. Marshall syndrome (OMIM: 154780), also caused by heterozygous mutation in *COL11A1*, may present with sensorineural hearing loss, Robin sequence, short stature, and early onset arthritis. However, Marshall syndrome is associated with more distinctive craniofacial features present through adulthood, which include ocular hypertelorism, midfacial retrusion, and anteverted nares [Baraitser, 1982; Brunner et al., 1994; Griffith et al., 1998; Martin et al., 1999]. In addition to the striking dysmorphic facial features noted in Marshall syndrome, individuals with fibrochondrogenesis (OMIM 228520) have marked shortening of the limbs, micromelia, broad ribs with methaphyseal cupping, bell-shaped thorax, metaphyseal flaring of the long bones, thin clavicles, small scapulae, fragmented distal tufts, trident acetabular roof, platyspondyly, and often die in early infancy from pulmonary hypoplasia [Winter et al., 1983]. While Stickler and Marshall syndromes are dominantly inherited, fibrochondrogenesis is most commonly recessively inherited [Tompson et al., 2010]. Although our patients were dysmorphic and had metaphyseal flaring of their long bones on x-ray resembling fibrochondrogensis, their mutation was dominantly inherited and their skeletal findings included a narrow thoracic shape without evidence of pulmonary hypoplasia. They had mildly shortened ribs without methaphyseal cupping and normally formed vertebrae that lacked the characteristic hypoplastic posterior and rounded anterior ends [Tompson et al., 2010]. Clavicles and acetabular roof were also normal. Please see Table I for a comparison of the other *COL11A1* syndromes in contrast to our patients.

These siblings are the first reported cases of a heterozygous mutation in *COL11A1* with a more severe skeletal dysplasia than that noted in Stickler or Marshall syndromes. The skeletal findings were less severe than those found in recessive fibrochondrogenesis. The 3 amino acids deleted in the collagen XI alpha-1 chain are highly conserved in avians, amphibians, and fish. PROVEAN analysis (J. Craig Venter Institute) predicts this is a deleterious mutation, with a score of −23. The cutoff is −2.5 for a phenotypically damaging mutation (Fig. 4). We hypothesize that this deletion results in a dominant negative effect due to a change in formation of collagen XI and its known interactions with collagen II and V, resulting in phenotypic abnormalities in cartilage and ocular vitreous [Alzahrani et al., 2012; Richards et al., 2010].

Several other heterozygous mutations in the triple helical domain of different collagen structures have been reported to be phenotypically detrimental. Tompson et al., describe two cases in which a deletion in the triple helical domain of the collagen XI alpha-2 chain (*COL11A2*) results in a fibrochondrogenesis-like phenotype, lethal in early infancy, indicating that similar disorders can result from either recessively or dominantly inherited *COL11A2* mutations [Tompson et al., 2012]. Furthermore, a point mutation affecting glycine residues in a triple helical domain of the alpha-1 (*COL1A1*) and alpha-2 (*COL1A2*) chains of type I collagen results in dominantly inherited Osteogenesis Imperfecta type I-IV [Pollitt et al., 2006]. Disruption in biosynthesis of collagen VI resulting from mutations in the triple helical domain of the alpha-1 chain (*COL6A1*) causes Bethlem myopathy and Ullrich congenital muscular dystrophies, both of which can be recessively or dominantly inherited [Tooley et al., 2010].

In congruence with previously published data as described above, the cases described here document a new dominantly inherited severe skeletal dysplasia with a phenotype similar to, yet milder than fibrochondrogenesis.

Identification of these cases contributes an additional diagnosis to the type XI collagenopathies subgroup, currently composed of a variety of syndromes, including Stickler syndrome, Marshall syndrome and fibrochondrogenesis, which further develops the understanding of the molecular function of *COL11A1*. Typically, recessive disorders of *COL11A1* are severe and lethal in the perinatal period while dominant conditions are milder and non-lethal. We describe dominant disease that is severe and was lethal, yet not during the perinatal period. This information is vital in the counseling of recurrence risk, especially in the cases of parental germ-line mosaicism, as demonstrated in our report. Furthermore, the survival of these infants through early infancy, as well as the lack of pulmonary hypoplasia, suggest the potential for interventions that may allow long-term survival.

CONCLUSION

We present two individuals heterozygous for *COL11A1* mutations with a phenotype that is distinct from fibrochondrogenesis, Stickler and Marshall syndromes. These cases not only reveal a novel dominantly inherited *COL11A1* mutation and skeletal dysplasia phenotype, but broaden the phenotypic heterogeneity of dominantly inherited collagenopathies. Further

analysis of similar cases resulting from abnormalities in *COL11A1, COL11A2*, and *COL2A1* genes are required to further delineate the spectrum of associated phenotypes.

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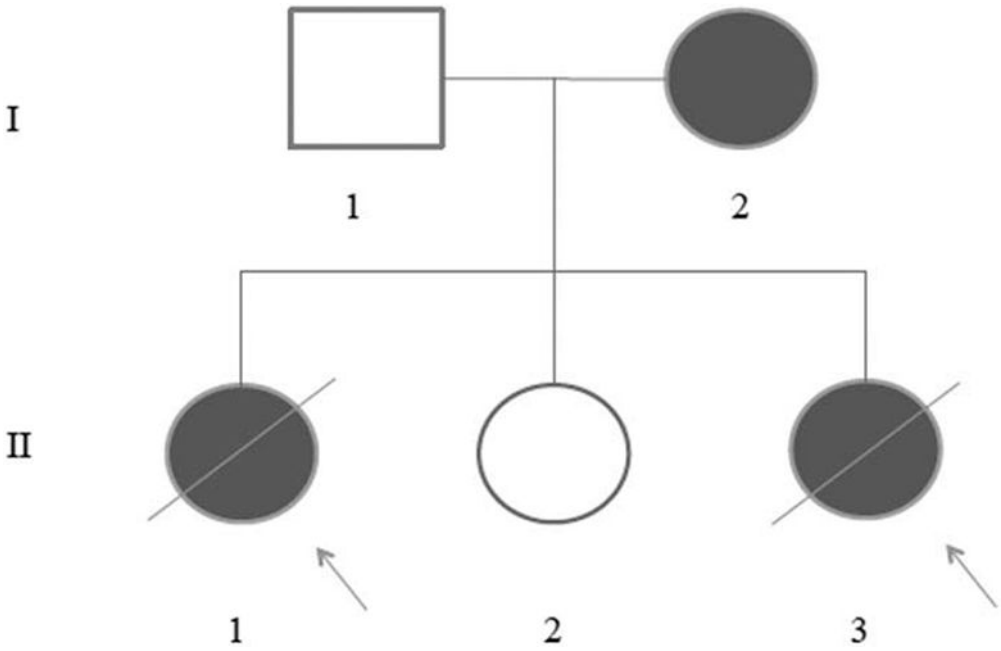
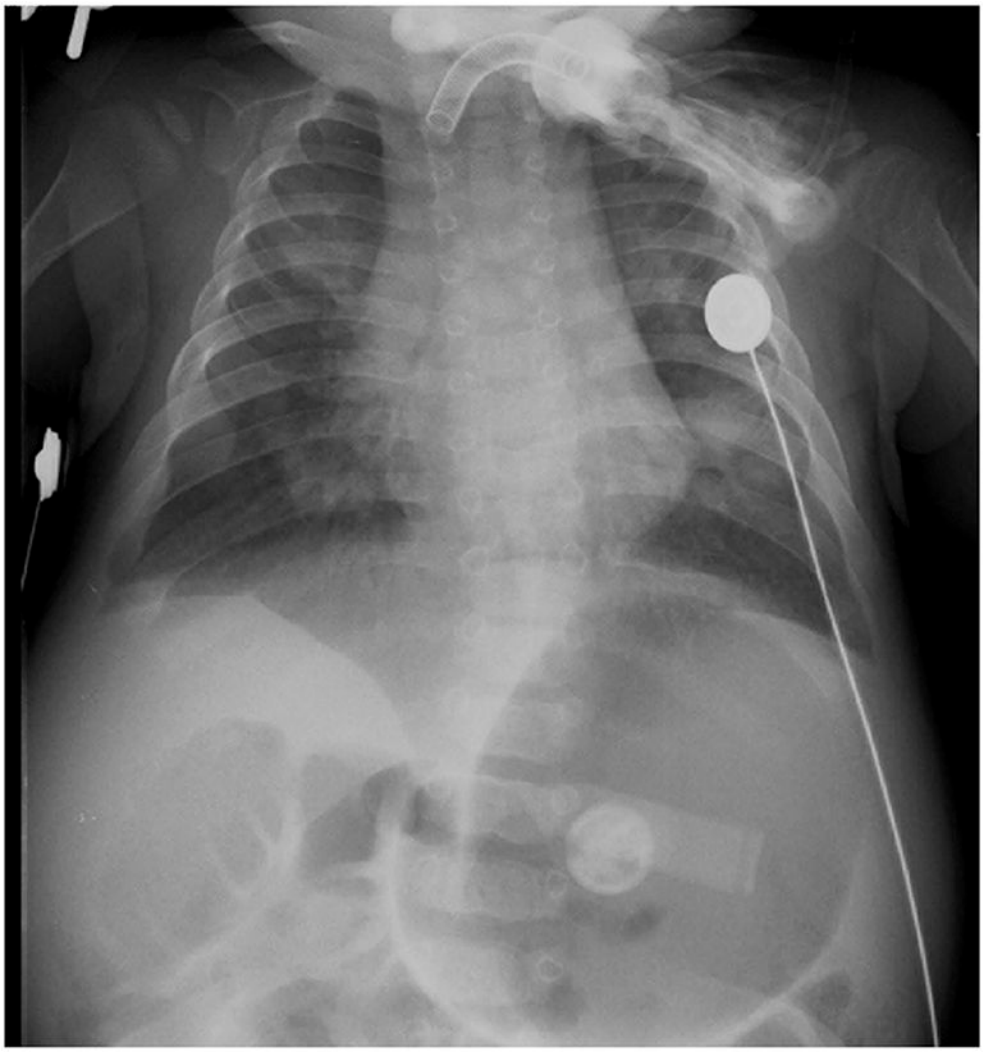


Figure 1:
Pedigree



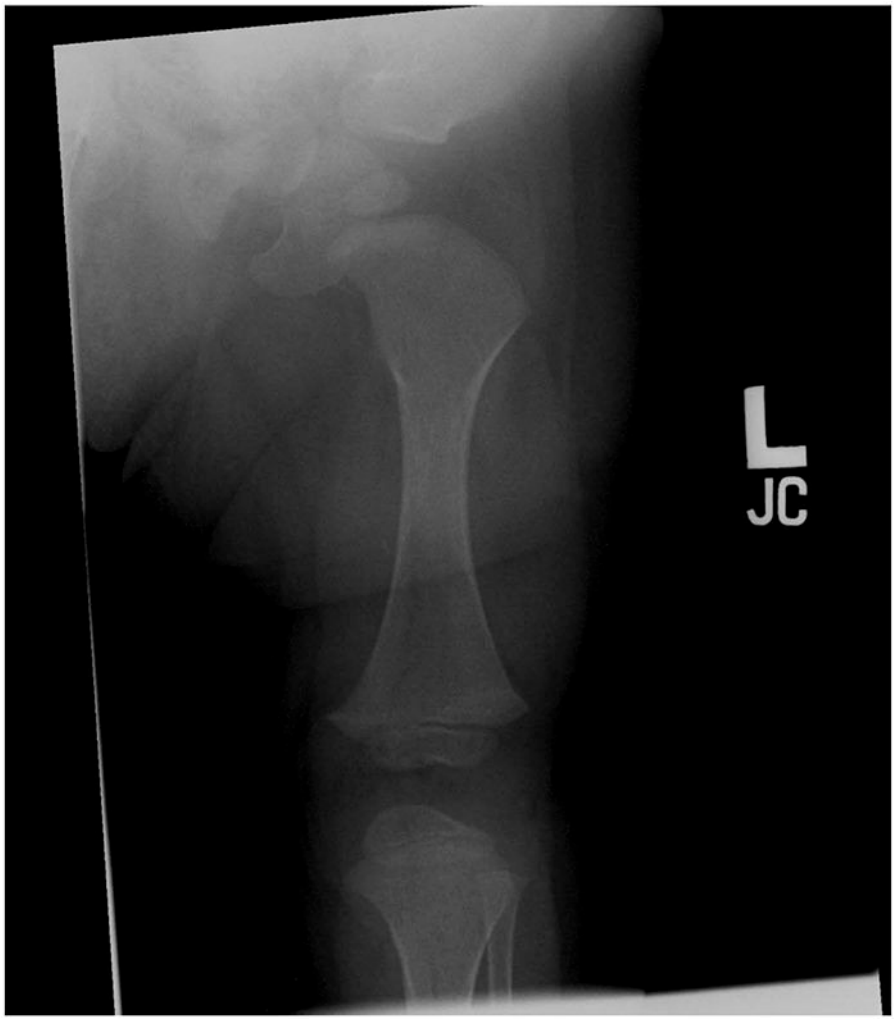
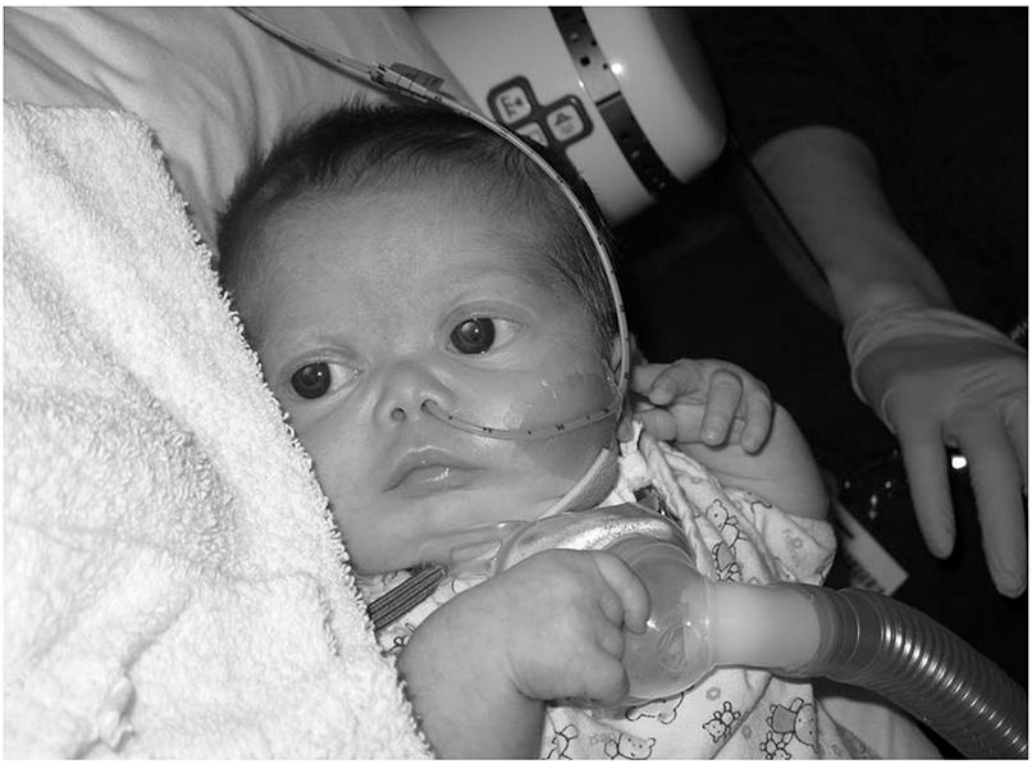


Figure 2:
X-ray for Patient 1. Figure 2a reveals a normal thoracic rib cage, ribs, and vertebrae but abnormally small scapulae. Figure 2b, the x-ray reveals a short, dumbbell shaped femur with metaphyseal widening.



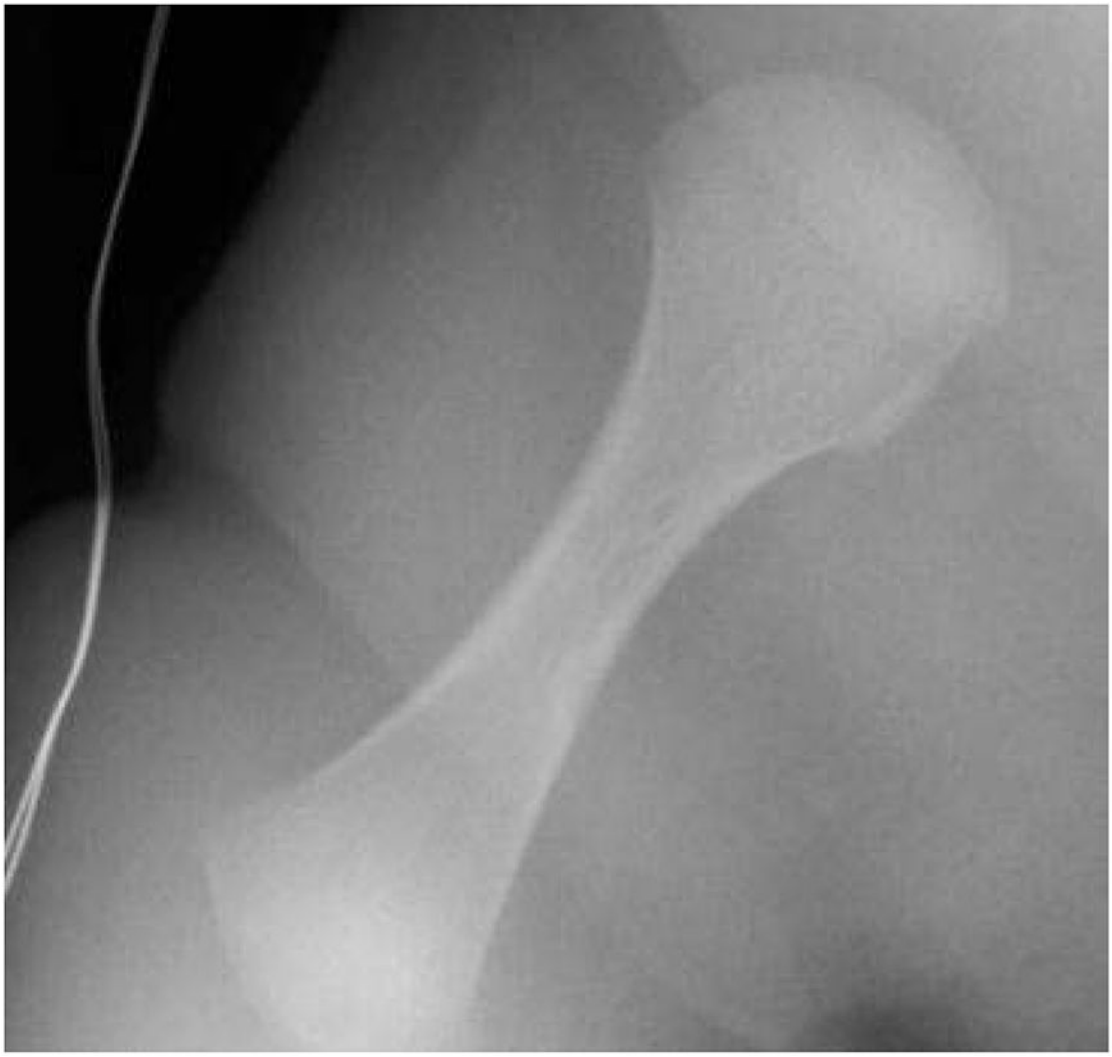


Figure 3:
Images of Patient II-3. Figure 3a highlights the dysmorphic features, which includes proptosis, anteverted nares, short nose, flat nasal bridge, midfacial retrusion, epicanthal folds and micrognathia. Features not seen in the image include frontal bossing, cleft palate, brachydactyly, and rhizomelia. The x-ray image in Figure 3b reveals a short, dumb-bell shaped femur with metaphysical widening.

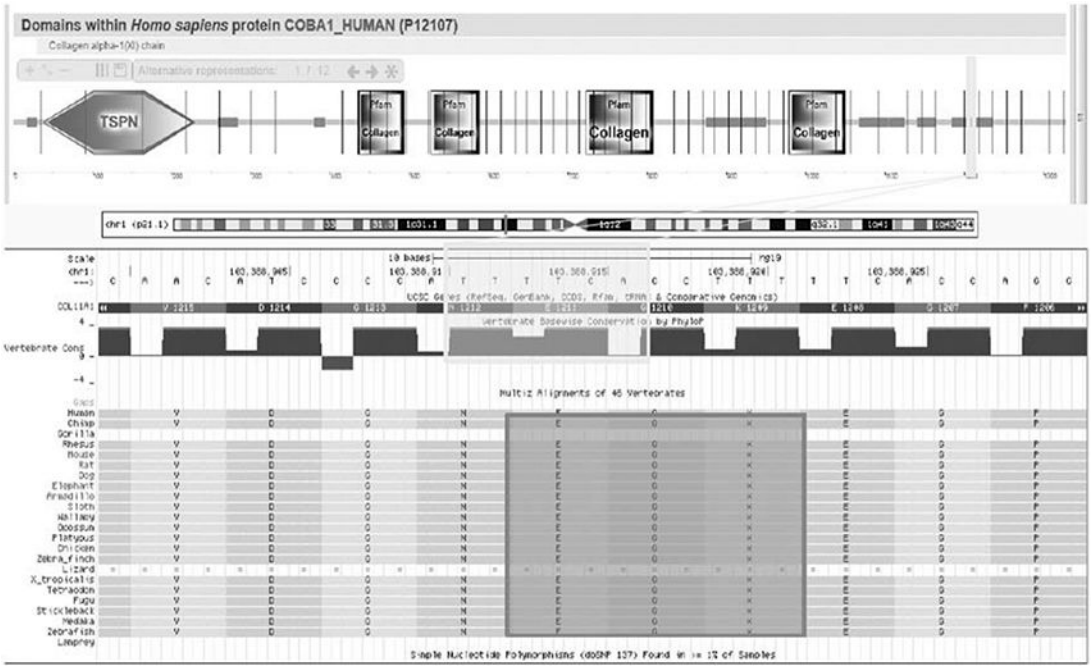


Figure 4:

SMART Protein model indicating the location of the *COL11A1* mutation in the triple helical domain. As illustrated by the utilization of UCSC Genome Browser, a deletion of 9bp (light grey box) results in an in-frame loss of 3 amino acids in the triple helical domain (dark grey box). The 9bp and 3 amino acids deleted are highly conserved in avians, amphibians, and fish. PROVEAN analysis predicts this is a deleterious deletion (score: −23, cutoff −2.5).

Table 1:

Comparison of Stickler, Marshall, Fibrochondrogenesis in contrast to our patients.

	Stickler syndrome	Marshall syndrome	Fribrochondro-genesis	Patients II-1 and II-3	Patient I-2, mother
Myopia	++	++	+	++	+
Midfacial retrusion	+	+	+	+	+
Micrognathia	+	+	+	+	+
Sensorineural hearing loss	+	+	Unk	+	−
Dysmorphic features	+	++	+	++	++
Bell shaped thorax	−	−	+	−	−
Rhizomelia	−	−	+	+	+
Abnormal ossification	−	+	+/−	−	−
Long, thin clavicles	−	−	+	−	−
Short, broad cupped ribs	−	−	+	−	−
Platyspondyly	−	−	+	−	−
trident acetabular roof	−	−	+	−	N/A
Small scapulae	−	−	+	+	N/A
Short, dumbbell long bones with metaphyseal widening	−	−	+	+	N/A
Fragmented distal tufts	−	−	+	−	N/A
Perinatal lethality	−	−	+	−	−
Inheritance	Dominant	Dominant	Recessive *	Dominant	Dominant

(+) present (−) absent (++) severe (N/A) information not available (Unk) unknown

*Most common inheritance pattern. Dominant inheritance is also noted in the literature [Tompson et al. 2012].