Clinical Case Report

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A novel sequence variant in *COL10A1* causing spondylometaphyseal dysplasia accompanied with coxa valga

A case report

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Abstract

Rationale: Spondylometaphyseal dysplasia (SMD) is an extremely rare disorder of irregular development of spine and metaphyses of long tubular bones. Mutations in the collagen type X alpha 1 gene were found to underlie this condition. Previously reported mutations in the N-terminal non-collagenous NC2 domain and C-terminal non-collagenous NC1 domain failed to be identified in some specific patients.

Patient concerns: A 23-year-old male was referred to us for fixed, angular thoracolumbar kyphosis with semi-paralysis, numbness, and tremor on his left lower limb. Marked hypoplasia of thoracolumbar vertebra and spinal canal stenosis were observed on radiology.

Diagnoses: He was diagnosed with spondylometaphyseal dysplasia (Type A4). Gene sequencing was performed using normalized targeted regions sequencing (TRS). A novel heterozygous missense variant p.Gly139Cys in the triple-helical region. Multiple lines of evidence imply this mutation to be pathogenic.

Interventions: Posterior instrumentation and vertebral column resection were given to correct his fixed, angular thoracolumbar kyphosis.

Outcomes: The correction was satisfying and the functional outcomes were good.

Lessons subsections as per style: The findings corroborated that type X collagen plays a critical role in the formation of the human spine as well as the long bones, and further expanded the range of type X collagenopathy. Surgical procedure could be considered for patients with severe malformation and neurological impairments.

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XZ carried out the genetic studies, participated in the sequence alignment, and drafted the manuscript. XS participated in the design of the study and performed the statistical analysis. WZ conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate: All procedures followed in this study were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000, and this project was approved by the local institution review board (Anhui Provincial Hospital Ethics Committee on Medical Research). For retrospective and non-interventional studies, reference numbers are not applicable according to local regulations. Informed consent was obtained for all participants included in the study.

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The authors declare that they have no competing interests.

Informed written consent was obtained from the patient for publication of this case report and accompanying images

Please contact author for availability of data and materials.

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Abbreviations: ACMG = American College of Medical Genetics and Genomics, BMD = bone mineral density, MCDS = Schmid-type metaphyseal chondrodysplasia, MR = magnetic resonance, PM = moderate pathogenicity, PP = supporting pathogenicity, PS = strong pathogenicity, SD = standard deviation, SMD = spondylometaphyseal dysplasia, TRS = targeted regions sequencing.

Keywords: *COL10A1*, gene mutation, spondylometaphyseal dysplasia, type X collagenopathy

1. Introduction

Spondylometaphyseal dysplasia (SMD) is a group of genetic skeletal disorders that show abnormal development of spine and metaphyses of long tubular bones. The main clinical features of axial SMD include: firstly, mild postnatal growth failure, secondly, severe chest deformity, and thirdly, impaired visual acuity with retinal dystrophy.[1,2] The radiological features of axial SMD include: firstly, cupped and flared anterior ends of ribs, secondly, lacyilia, and thirdly, metaphyseal dysplasia of proximal femora with irregular and enchondroma-like metaphyses.[2] The genetic etiology of SMD is currently unknown, whereas the mutations in type X collagen gene (*COL10A1*) were considered excellent candidates,[3] because type X collagen is a cartilage-specific short-chain collagen[4] that is expressed specifically in hypertrophic zones of the growth plate.[5] Previously reported mutations in the N-terminal non-collagenous NC2 domain and C-terminal non-collagenous NC1 domain failed to be identified in some specific patients.[3,6] Here, we add a new novel variant in the *COL10A1* gene mutation spectrum through gene sequencing analysis in a patient of Chinese origin.

2. Case report

A 23-year-old male was the second born to a third-degree consanguineous married couple (Fig. 1A). He weighed 3.0 kg at birth (median = 3.35, SD = 0.42). He was walking at 18 months old and his psychomotor development was otherwise normal. His development was age appropriate until 5 years old when coxa valga and mild spinal kyphosis were discovered. His patients had consulted to local physicians and conservative methods were given, for example, orthosis, etc. The therapeutic protocol was not fully complied during his growth history. He was referred to us at 23 years old for fixed, angular thoracolumbar kyphosis. At initial presentation, he had only mild back complaint and slightly walking lame on both sides. Half a year after his first consultation, he came back to us for semi-paralysis, numbness, and tremor on his left lower limb. On examination his height was 147 cm and his weight was 45 kg, 2 SD less than the average of peers in same age, while his head circumference was normal (56 cm). He showed obvious malformed chest with scoliosis and local kyphosis at the thoracolumbar junction (Fig. 1B). The radiological examination showed moderate scoliosis and severe angular kyphosis at the thoracolumbar junction. Vertebral dysplasia was found at all levels of the spine. In particular, marked hypoplasia of L1 vertebra and beaking of T11 and T12 vertebrae were observed (Fig. 2A). Caudal stenosis and cord compression were found on the MR images (Fig. 2B). Flexion and extension cervical radiographs showed no instability or hypoplasia of the odontoid, however, his cervical vertebral physiological curvature became straight and the cervical vertebral canal was relatively narrow.

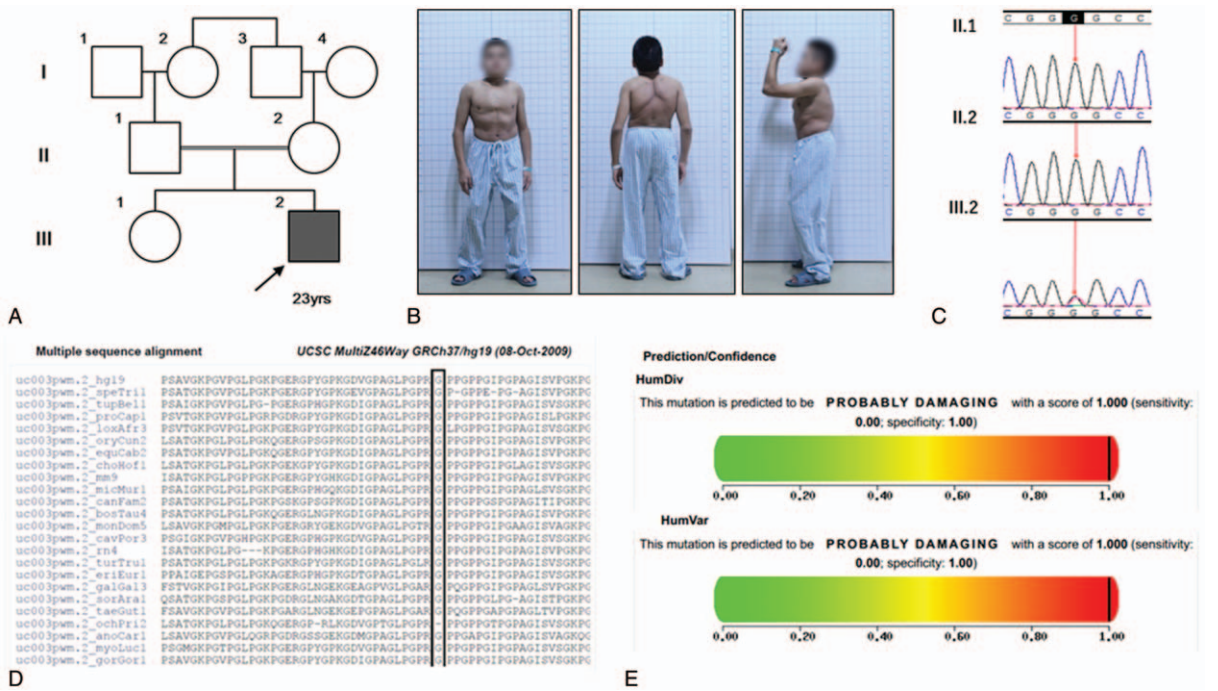

Figure 1. Pedigree shows consanguineous union of parents (A). The patient showed obvious malformed chest with scoliosis and local kyphosis at the thoracolumbar junction (B). The variant p.Gly139Cys in exon 3 of *COL10A1* gene shows Mendelian segregation (upper panel: father, middle: mother, lower: proband) (C). Sequence alignment shows the G139 is identical among different species (D). The PolyPhen-2 software reported a deleterious mutation effect in multiple lines (E).

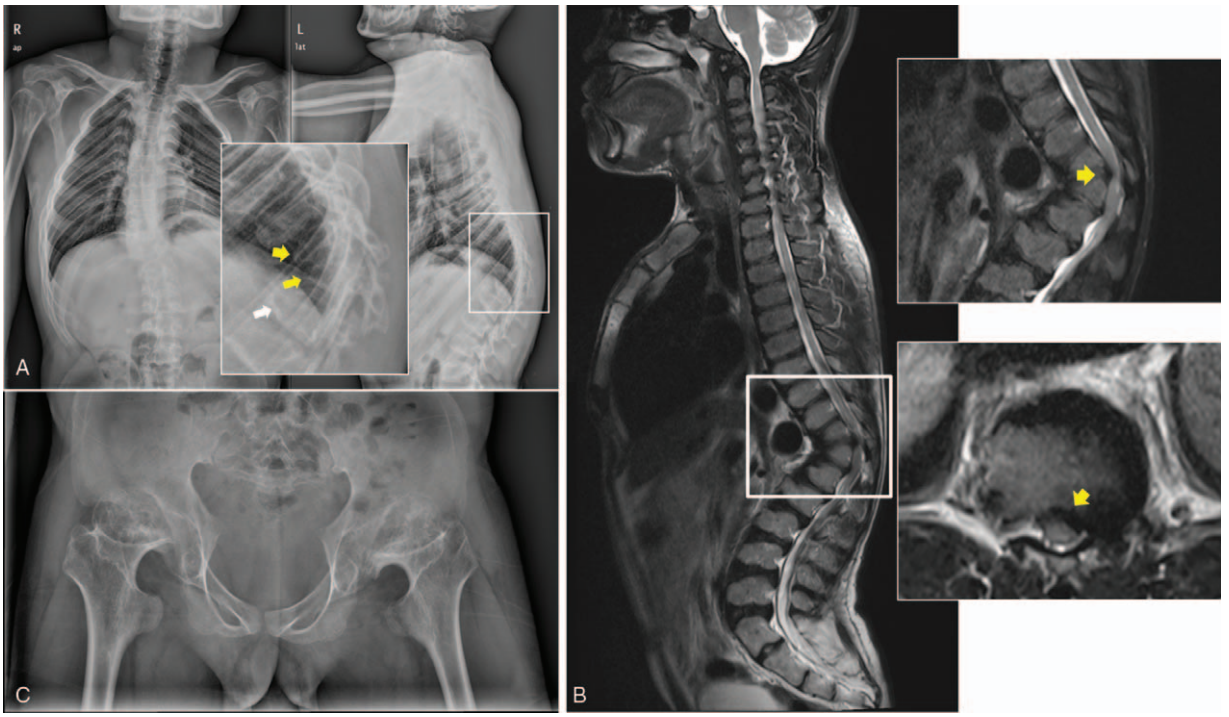

Figure 2. Radiographs of this 23-year-old male showed obvious malformed chest and kyphosis at the thoracolumbar junction, with marked hypoplasia of L1 vertebra and beaking of T11 and T12 vertebras (A). MRI images indicate caudal stenosis and cord compression at T11/12 level (B). Pelvic plain film showed widening metaphyseal with thinning of cortices, coxa valga and congenital dysplasia (C).

Both of his bilateral hips showed severe coxa valga with congenital dysplasia and dislocation (Fig. 2C). Widened metaphyses with cortical thinning of his long bones were found at humerus and femurs on both sides. He was clinically diagnosed to have spondylometaphyseal dysplasia (Type A4).

Low bone mineral density (BMD) was observed in this case ($Z=-2.2$, $Z_{fn}=-3$, $Z_{wt}=-3.3$, and $Z_{gt}=-2.7$). His serum calcium and bone metabolic markers were detected to be almost within normal range. Markers of bone turnover were also tested and taken into consideration. (Table 1)

The proband was clinically evaluated and recruited for the study after obtaining informed consent from him and his family.

Table 1

Bone mineral density, metabolic markers, and turnover markers tests in this case.

		Value	Reference range
BMD (*Z*-value)	Overall (*Z*)	−2.2	–
	Femoral neck (Z_{fn})	−3	–
	Wards triangle (Z_{wt})	−3.3	–
	Great trochanter (Z_{gt})	−2.7	–
Metabolic markers	Serum calcium (Ca, mmol/L)	2.13	2.03–2.54
	Vitamin D (Vit D, ng/L)	28.52	26–65
	Calcitonin (CT, ng/L)	2.4	<14
	Parathormone (PTH, pmol/L)	8.7	1–10
Turnover markers	Alkaline phosphatase (ALP, U/L)	54	40–160
	Total propeptide of type 1 procollagen (P1NP, μg/ml)	59.73	–
	β-carboxyl-terminal cross-linked telopeptide of type I collagen (β-CTX, μg/ml)	1.48	–

Gene sequencing was performed using normalized targeted regions sequencing (TRS). Mutation in the *COL10A1* coding region was identified comparing to the normal population reference (NM_000493.3). Sanger sequencing was done for further validation. In silico analysis was performed with PolyPhen-2 tool (http://genetics.bwh.harvard.edu/pph2/).[7] Data analysis was performed referring to the human genome reference UCSC hg19 Feb.2009. The sequencing explanation was performed according to the American College of Medical Genetics and Genomics (ACMG) guidelines. The study had the approval of the local ethics committee.

The TRS sequencing of *COL10A1* gene revealed a novel heterozygous missense variation in Exon 3 of *COL10A1* gene, c.415G>T, leading to a translation error at amino acid 139 (p. Gly139Cys). It is predicted to be disease causing by in silico analysis. Validation by Sanger sequencing in his parents confirmed de novo mutation (Fig. 1C).

This patient received posterior instrumentation and vertebral column resection to correct his fixed, angular thoracolumbar kyphosis. The correction was satisfying and the functional outcomes were good. Anti-osteoporosis management was initialized soon after operation. A postoperative pathology showed deteriorated chondrocytes and comparative normal osteocytes. The nucleus pulposus was severely deteriorated and partially calcified.

3. Discussion

Spondylometaphyseal dysplasia represents a heterogeneous group of bone dysplasia characterized by vertebral and metaphyseal abnormalities as well as a short stature. It is divided into three main groups according to femoral neck involvement,

and further subdivided into nine types according to the vertebral and metaphyseal involvement.[8] In the present case, we report a case with severe coxa valga and tongue-like flattened vertebral bodies, which conform to the Type A4 mostly.

The *COL10A1* gene encodes the alpha chain of type X collagen, a short non-fibrillar chain in the homotrimer collagen expressed by hypertrophic chondrocytes during endochondral ossification. Mutation in *COL10A1* was previously reported in patients with Japanese-type SMD.[9] The mutation occurred in the C-terminal globular domain of the gene (G>A transversion at NT 1784 in one allele) and resulted in the substitution of a glutamic acid residue for a glycine at codon 595 (G595E). However, screens failed to identify such mutation in patients with Kozlowski type and corner fracture type SMD,[6] even other subject diagnosed with Japanese-type SMD.[3] Other mutations are mostly found in the C-terminal globular domain (NC1 domain), which is the important region in Schmid-type metaphyseal chondrodysplasia (MCDS).

In this study, we found a novel heterozygous missense variation in triple-helical region of *COL10A1* gene. We detected a G>T transversion at c.415 in one allele. The mutation occurred in the triple-helical region of the gene and resulted in the substitution of a cysteine acid residue for a glycine (G139C). The G139 of type X collagen is highly conserved. A sequence comparison of the triple-helical region revealed that G139 is identical among squirrel (speTri1), mouse(mm9), rat(rn4), bovine(bosTau4), erinaceus europaeus (eriEur1), and canine (canFam2), etc (Fig. 1D). The mutation was confirmed absent from controls in Exome Sequencing Project, 1000 Genomes Project and Exome Aggregation Consortium. Multiple lines of computational evidence support a deleterious effect on the gene mutation (Fig. 1E). Further Sanger validation in his patients confirmed de novo mutation with no family history. Thus, three lines of evidence lead to the conclusion that the G139C mutation likely pathogenic in this family (PS2+PM+PP*), according to the latest ACMG guidelines.[10]

Typically osteoporosis was not the top concern among SMD patients since they are mostly found in children and treated conservatively.[11] We found in the case severe low BMD level occasionally before surgery, while bio-makers and postoperative pathologic findings didn't support a mineral metabolic disorder. Although some of the collagen encoding genes revealed relevance with osteoporosis, we attribute it more to a symptom of disuse osteoporosis. Apparently it is the endochondral defect ossification that makes SMD a unique disorder, thus the deterioration of chondrocytes was considered the main pathophysiologic change in this disease.

We reported a first case with a novel variant that might activate missense-mediated mRNA decay at the 139st amino acid residue or result in a transcribed but not fully-functioning protein. To the best of our knowledge, such mutation hasn't been reported in literature. Our observation presents in vivo also corroborated that type X collagen plays a critical role in the formation of the human spine as well as the long bones. Mutations of *COL10A1* could lead to a phenotypic spectrum that includes Schmid MCD and SMD. The full extent as well as the pathological mechanism of type X collagenopathies should be clarified by additional studies. We hereby added one new sequence variant into the growing spectrum of *COL10A1* gene mutations causing SMD disease, which expanded the range of pathological phenotypes produced by the aberration of type X collagen (type X collagenopathy).

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* PS: strong pathogenicity; PM: moderate pathogenicity; PP: supporting pathogenicity.