A novel homozygous variant of COL2A1 in a Chinese male with type II collagenopathy: a case report

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Abstract

Background: Type II collagenopathies are a spectrum of diseases and skeletal dysplasia is one of the prominent features of collagenopathies. Molecular defects of the COL2A1 gene cause type II collagenopathies that is mainly an autosomal dominant disease, whereas some rare cases with autosomal recessive inheritance of mode have also been identified.

Case presentation: The patient was a 5-year-old male with a short neck, flat face, epiphyseal dysplasia, irregular vertebral endplates, and osteochondritis. Sequencing result indicated NM_001844.4: c.3662C > T; p. (Ser1221Phe) a novel missense variant, leading to a serine-to-phenylalanine substitution. Sanger sequencing confirmed the variant compared to his parents and brother.

Conclusions: We identified a novel homozygous variant of the COL2A1 gene as the cause of type II collagenopathies in a Chinese male, enriching the spectrum of genotypes. This is the first case of type II collagenopathies inherited in an autosomal recessive manner in China and East Asia, and it is the first case that resulted from serine substitution in the world.

Keywords: Type II collagenopathies, COL2A1 gene, Whole-exome sequencing, Novel variant, Rare complex syndrome

Background

Type II collagenopathies are a series of diseases characterized by skeletal dysplasia [1]. The clinical symptoms are notably variable, including short stature, eyesight abnormality, hearing loss, kyphosis, and epiphyseal dysplasia. According to the variety and severity of their symptoms, patients are classified into 21 different phenotypes [2] such as Stickler syndrome type I (STL1, MIM#108300) and Spondyloepiphyseal dysplasia congenita (SED, MIM#183900), though clinical presentations of these phenotypes overlap considerably. Type II collagenopathies are resulted by mutation of COL2A1 (MIM #120140) and are inherited in an autosomal dominant manner. Recently, autosomal recessive inherence was identified in patients with type II collagenopathies: all of the patients were from West Asia [3–6], probably owing to a higher rate of consanguinity and extensive development of gene sequencing.

The COL2A1 gene, which is located in the 12q13.11 region, contains 54 exons and encodes the alpha-1 chain of procollagen type II [7]. It is specifically expressed in the vitreous, cartilage, inner ear, and intervertebral discs, which explains the typical clinical features of type II
collagenopathies [8, 9]. The protein encoded by \textit{COL2A1} contains a typical triple-helical domain and a C-terminal region where variants have been found previously. The triple-helical domain comprises Gly-X-Y repeats, which is a typical feature of collagens. Most variants found in patients with type II collagenopathies are located in the triple-helical domain and Gly substitutions in this domain are usually related to severe phenotypes [2].

In the present study, whole-exome sequencing (WES) was performed on DNA sample obtained from one Chinese patient manifesting a short neck, flat face, epiphysseal dysplasia, irregular vertebral endplates, and osteochondritis. A novel homozygous variant of the \textit{COL2A1} gene was identified and the patient was diagnosed with type II collagenopathy. This is the first case of a patient with a \textit{COL2A1} homozygous variant in China and in East Asia. It is also the first case that resulted from a serine substitution worldwide.

**Case presentation**

The patient was a 5-year-old male with a birth length of 51 cm (+0.33SD) and a birth weight of 4000 g (+1.65SD). He is the second child of a non-consanguineous healthy couple and was delivered by caesarean section at 40 weeks. Development was normal before one and a half years of age; subsequently, lower-limb abnormality and short stature were noticed. Since three years of age, he has been suffered from consistent low bone mineral density (Z:1.6~ −2.4, 1−5%) which could not be corrected by calcium and vitamin D supplementation. He occasionally complained of ankle ache after exercise. At 5 years of age, he was referred to our department due to the manifested bone abnormality. Physical examination showed a flat face, short neck, short lower limbs especially under the knees, brachydactyly, enlargement of the medium interphalangeal joints with normal height (105.8 cm, −1.29SD) and weight (24 kg, +1.87SD) (Fig. 1A−F). The patient had normal hearing, vision, cognitive development, and expression ability. Chest computed tomography and urinary system ultrasound were normal. X-ray of the spine showed that platyspondyly with irregular vertebral endplates, and bone defects were observed on the top of T12 (Fig. 1G, H). X-ray of the knees and hand confirmed the results found on physical examination (Fig. 1I, J) and that of the pelvis revealed a heterogeneous bone structure of the proximal femur (Fig. 1K). Magnetic resonance imaging of the right ankle showed signs of osteochondritis (Fig. 1L, M).

Laboratory investigations revealed normal levels of liver function, renal function, erythrocyte sedimentation rate, thyroid function, and levels of parathyroid hormone and serum calcium. Additionally, the patient showed elevated levels of alkaline phosphatase (184 IU/L, reference range: 45−129 IU/L) and serum inorganic phosphorus (1.8 mmol/L, reference range: 0.78−1.65 mmol/L). Further, myocardium zymogram examination revealed that creatine kinase isoenzyme-MB (4.8 μg/L, reference range: <3.7 μg/L) and creatine kinase isoenzyme (193 U/L, reference range: 55−170 U/L) levels were above the normal.

The patient’s father was 173 cm, and his mother was 156 cm in height; both parents were healthy. He also had an 8-year-old healthy brother, with a height of 130.5 cm (Fig. 2A). The parents’ and the only brother’s spines, pelvises, and knees were evaluated using X-ray and no abnormality was observed (Additional file 1: Figs. S1, S2, S3).

WES was performed on the proband. Sequencing was performed and clusters were generated with an Illumina HiSeq 2000 system (Illumia, Inc.) and an Illumina cBot system (Illumina Inc., San Diego, CA, USA) respectively. The average read depth was 162.91X (Additional file 1: Table S1). All variants were annotated and filtered by Ingenuity Variant Analysis (Ingenuity Systems, Redwood City, CA, USA). Candidate variants were analyzed while skeletal dysplasia was selected as the main filtering symptom. Among all filtered variants, a homozygous missense variant in \textit{COL2A1} was confirmed and explained the patient’s condition (PM2+PP3+PP4), according to the guidelines recommended by the American College of Medical Genetics and Genomics (ACMG) (Additional file 1: Table S2). The novel variant NM_001844.4: c.3662C>T in \textit{COL2A1} led to a serine-to-phenylalanine substitution. Sanger sequencing indicated that the parents and brother were heterozygous for this variant (Fig. 2A, B).

Using in silico tools, we evaluated the pathogenicity of the variant of the \textit{COL2A1}. The position of the variant is highly conserved in multiple species (Fig. 2C). Functional prediction indicated that the variant has a deleterious effect on the protein according to PolyPhen-2 (probably damaging, score = 0.99), SIFT (damaging, score = 0.003), and MutationTaster (disease causing, score = 1). To better assess the pathogenicity, a three-dimensional model was generated and examined using the I-TASSER server[10] (http://zhanglab.ccmb.med.umich.edu/I-TASSER) and Pymol v.1.8.4.0 software (https://www.pymol.org; Schrödinger, New York, NY, USA) respectively (Fig. 3). Normally, the amino acid residue serine is highly conserved in the triple-helical domain and Gly substitutions in this region where variants have been found previously. The triple-helical domain comprises Gly-X-Y repeats, which is a typical feature of collagens. Most variants found in patients with type II collagenopathies are located in the triple-helical domain and Gly substitutions in this domain are usually related to severe phenotypes [2].

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Discussion and conclusions

In the present study, since the observed phenotype was not completely typical for collagenopathy, WES was considered for diagnosis based on its wide coverage and not cost-incurring performance. We successfully identified a novel homozygous variant of the \textit{COL2A1} gene in a Chinese patient with type II collagenopathy. The variant c.3662C > T was located in exon 51 and could result in a serine-to-phenylalanine substitution in the C-terminal region. Both parents of the proband were heterozygous for this variant. The allele frequency of the variant was absent from the gnomAD database (http://gnomad.broad institute.org/) and the 1000 Genomes Project (http://www.1000genomes.org). To the best of our knowledge, this is the first report of a variant resulting in serine replacement in \textit{COL2A1}. Additionally, pathogenicity confirmed by in silico studies and the highly conserved protein and nucleotide sequences implied that this variant was disease-causing. Though the variant is classified as a variant of uncertain significance according to ACMG guidelines, a high correlation between this variant and the mild phenotype of type II collagenopathy was observed.

To date, 514 variants of the \textit{COL2A1} gene have been reported in the human gene mutation database (http://www.hgmd.cf.ac.uk/ac/), including 241 missense
variants, 95 splicing variants, 31 nonsense variants, 93 small deletions, 32 small insertions, and 22 other variants such as gross deletions / insertions / duplications and complex rearrangements. As mentioned above, mutations in the COL2A1 gene are mainly autosomal dominant although an autosomal recessive inheritance manner was reported in recent years. All reported
COL2A1 variants with autosomal recessive inheritance are shown in Fig. 4.

To demonstrate a genotype–phenotype correlation, we collected the clinical information of all patients with homozygous missense variants (Table 1) and analyzed the data by domains (Additional file 1: Table S3). We also compared these data with that of heterozygous variants.

Vertebral abnormality, such as irregular vertebral endplates and platyspondyly could be observed in almost all patients with homozygous missense variants. Platyspondyly is also a common feature in different phenotypes of type II collagenopathy inherited in a heterozygous manner [2]. Eyesight abnormality, kyphosis, scoliosis, and waddling gait only occur in patients with mutations in the triple-helical domain. However, in cases with heterozygous mutations, these symptoms are not specifically associated with mutations in the triple-helical domain. Additionally, glycine substitution was highly relevant to SEDC [11]. Glycine substitution usually leads to an abnormal conformation or destabilization of the triple helix, thereby acting in a dominant-negative way [2]. No glycine substitution has been reported in patients with homozygous variants to date.

Variants in the C-terminal region could also affect collagen formation. Patients with mutations in the C-terminal region present with milder phenotypes with some characteristic symptoms, probably because the variant has limited influence on the mature type II collagen [11]. Brachydactyly, especially of the middle and distal phalanges, seems to be the most common clinical feature of variants in the C-terminal region [3, 12], which was also observed in the present case. Further, variants in the C-terminal propeptide are also associated with platyspondylic skeletal dysplasia Torrance type (MIM#151210) and with Spondyloperipheral dysplasia (SPPD, MIM#271700) [13]. Based on the present case, serine substitution in the C-terminal region seems to have no relation with severe phenotypes; however, there is not enough data reported on serine substitution at this time to make a definitive conclusion.

Our data collection and analysis may provide more insights into the phenotype of type II collagenopathy, especially for patients with homozygous missense variants. Tham et al. [5] reported the first patient with a homozygous variant and assumed the relationship between the bi-allelic variant of COL2A1 and SEDC. This was supported by Barat-Houari et al. [4], who described a more severe patient with SEDC with homozygosity. However, Girisha et al. [3] then reported four patients with bi-allelic variants in COL2A1 which rarely caused SEDC. In type II collagenopathies dominantly inherited, more than 100 COL2A1 variants have been reported in patients diagnosed with SEDC, and most of the variants are located in the triple-helical domain (74% Gly replacements and 10% Arg-to-Cys substitutions) [14]. Our patient had mild abnormalities of the vertebrae with no hearing or ocular involvement, which shows that the case had a limited correlation with SEDC. Similar to autosomal dominant cases, different domains and amino acid substitutions should be considered. SEDC is not a homozygous variant-specific phenotype.

We also noticed that the patient’s height was within the normal range, whereas all of the previously reported cases had short stature at the last evaluation. Tham et al. [5] described detailed height information of a patient from birth to 11 years of age; height at birth was variable. Short stature in recessively inherited patients seems to become more severe as the patient gets older, indicating that height influence on the patient is probably cumulative. However, in patients with heterozygous mutations in the C-terminal propeptide, height clustered around the average level [13]. There is no specific relationship between height and domains in patients with homozygous variants. The proband’s height should be monitored closely.

It should be noted that all patients with homozygous variants were from consanguineous families in West
Table 1  Clinical manifestations of patients with type II collagenopathies with homozygous mutations

| Family | Patient | Sex | Age at onset | Age at diagnosis (genetic confirmation) | Consanguinity | Ethnicity | Birth height (cm)/weight (kg) | Height (cm)/weight (kg) at last evaluative | Eyesight abnormality | Hearing impairment | Short limbs | Brachydactyly | Motor delay | Short neck | Flat face | Irregular vertebral endplate | Platspondyly | Lumbar lordosis | Kyphosis | Scoliosis | Epiphyseal dysplasia | Metaphyseal enlargement | Joint pain/stiffness/laxity | Waddling gait | Others |
|--------|---------|-----|--------------|----------------------------------------|---------------|----------|-------------------------------|------------------------------------------|----------------------|-------------------|-------------|--------------|------------|-----------|---------|-----------------------------|-----------|-----------------|----------|----------|----------------------|------------------------|--------------------|--------------|---------|
| 1      | 1       | Male| 1.5 years    | nd                                     | +             | Chinese | 51 (+0.33SD)/4 (+1.6SD)       | 105.8 (−1.29)/24 (+1.87)                   | –                    | –                 | –           | –            | –          | –         | –       | –                           | +         | –               | –         | –        | –                    | –                      | –                 |
| 2      | 2       | Male| 2 years      | nd                                     | +             | Indian  | 49 (−0.85SD)/3.1 (−0.95SD)    | 117.5 (−4.85SD)/nd                         | + (−6.5/−7.5D)       | +                 | +           | +            | –          | –         | +       | +                           | +         | +               | –         | –        | –                    | –                      | –                 |
| 3      | 3       | Male| 24 weeks (gestational age) | 24 years                             | +             | Indian  | 38.5 (−4.5SD)/2.7 (−1.55SD)   | 68 (−4SD)/9.5 (−4.5)                        | + (−1OD)             | –                 | –           | +            | +          | –         | –       | +                           | +         | –               | –         | –        | –                    | –                      | –                 |
| 4      | 4       | Male| nd           | nd                                     | +             | Indian  | nd                           | 97 (−11)/nd                                | –                    | –                 | –           | –            | –          | –         | +       | +                           | +         | –               | –         | –        | –                    | –                      | –                 |
| 5      | 5       | Male| nd           | nd                                     | +             | Indian  | 127 (−2)/20 (−2.8)            | 104 (−10)/nd                               | –                    | –                 | –           | –            | +          | +         | –       | +                           | +         | +               | –         | +        | –                    | –                      | +                 |
| 6      | 6       | Female| 3 years | 7 years                             | +             | Indian  | nd                           | nd                                       | –                    | –                 | –           | –            | +          | +         | –       | +                           | +         | +               | –         | –        | –                    | –                      | +                 |
| 7      | 7       | Male| 10 years     | 10 years                               | +             | Indian  | nd                           | nd                                       | –                    | –                 | –           | –            | +          | +         | –       | +                           | +         | +               | –         | –        | –                    | –                      | +                 |

| Identified variant | Exon | Domain | Reference |
|-------------------|------|--------|-----------|
| c.3662C>T (p.Ser1221Phe) | 51   | C-terminal | This study |
| c.1309C>T (p.Arg437Trp) | 21   | Triple helical domain | Tham, E., et al |
| c.1373C>T (p.Pro458Leu) | 22   | Triple helical domain | Barat-Houari, M., et al |
| c.4135C>T (p.Arg1379Cys) | 53   | C-terminal | Girisha, K. M. et al |
| c.4135C>T (p.Arg1379Cys) | 47   | Triple helical domain | |
| c.3190C>T (p.Arg1133Cys) | 47   | Triple helical domain | |

nd, no data
Asia, except for our patient. Thus, the carrying rate of COL2A1 in Chinese may be underestimated.

In conclusion, this study reported the first Chinese patient with type II collagenopathy with autosomal recessive inheritance, thereby enriching the spectrum of genotypes. The patient presented with a mild phenotype. With the rapid development and application of sequencing technologies, we believe that more variants relating to milder phenotypes will be identified. However, direct functional evidence is lacking to prove the pathogenicity of all variants inherited in an autosomal recessive manner. The precise genotype–phenotype correlation and specific mechanisms remain unknown and require further study.

Abbreviations
STL1: Stickler syndrome type I; SPPD: Spondyloperipheral dysplasia; SEDC: Spondyloepiphyseal dysplasia congenital; WES: Whole-exome sequencing; ACMG: American College of Medical Genetics and Genomics.

Supplementary Information
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Authors’ contributions
XW designed the study; QZ drafted and revised the manuscript; RY revised the manuscript. QZ, QL, XL, BF, GC, and JW acquired, analyzed, and interpreted the data. All authors read and approved the final manuscript.

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Availability of data and materials
The variant has been submitted to the NCBI ClinVar database whose accession number is SCV001755682. The raw sequence datasets generated during the current study are not publicly available because it is possible that individual privacy could be compromised but they are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
The study was approved by the Ethics Committee of Shanghai Children’s Medical Center (SCCMIRB-Y2019049), Shanghai Jiao Tong University School of Medicine. Written informed consent to participate was obtained from the patient’s parents.

Consent for publication
Written informed consent for publication of identifying images and other personal or clinical details was obtained from the patient’s parents. And the copy of the written consent is available for review by the editor of this journal.

Competing interests
The authors declare no conflict of interest.

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