Novel *COL11A2* Pathogenic Variants in a Child with Autosomal Recessive Otospondylomegaepiphyseal Dysplasia: A Review of the Literature

Pavalan Selvam[1] Shekhar Singh[1] Angita Jain[1] Herjot Atwal[1] Paldeep S. Atwal[1]

[1] Department of Clinical and Biochemical Genetics, The Atwal Clinic: Genomic & Personalized Medicine, Jacksonville, Florida, United States

J Pediatr Genet 2020;9:117–120.

Address for correspondence Paldeep S. Atwal, MD, FACMG, FRCP (UK), FRCP(Glasg), Department of Clinical and Biochemical Genetics, The Atwal Clinic: Genomic & Personalized Medicine, Jacksonville, FL 32246, United States (e-mail: DrA@AtwalClinic.com).

Abstract

Otospondylomegaepiphyseal dysplasia (OSMED) is an inherited autosomal dominant and recessive skeletal dysplasia caused by both heterozygous and homozygous pathogenic variants in *COL11A2* encoding the α2(XI) collagen chains, a part of type XI collagen. Here, we describe a 2-year-old girl presenting from birth with a phenotype suggestive of OSMED. On whole exome sequence analysis of the family via commercially available methods, we detected two novel heterozygous pathogenic variants in the proband. In addition, we reviewed the phenotype of autosomal recessive OSMED cases with *COL11A2* pathogenic variants reported to date and quantitatively highlighted the phenotypic spectrum.

Keywords

- otospondylomegaepiphyseal dysplasia
- autosomal recessive
- *COL11A2*

Introduction

Otospondylomegaepiphyseal dysplasia (OSMED) is a rare inherited disorder characterized by both autosomal dominant and recessive inheritance patterns.[1] The autosomal recessive OSMED type B (OMIM: 215150) was referred to as Weissenbacher–Zweymuller syndrome (WZS), Nance–Insley syndrome, Nance–Sweeney chondrodysplasia, and chondrodystrophy with sensorineural deafness. Patients diagnosed with OSMED type B have been described with short, disproportionate limbs, vertebral defects such as coronal clefts, platyspondyly, mega epiphysis, dumbbell femurs, squared iliac wings, and metaphyseal flaring in the radiograph, enlarged joints, early osteoarthritis, dysmorphic features such as the depressed nasal bridge, midface hypoplasia, micrognathia, cleft palate, and sensorineural deafness along with an absence of ocular findings such as high myopia, cataracts, retinal detachment, and vitreoretinal degeneration.[2,3]

Pathogenic variants in *COL11A2* have been established as the pathogenesis behind OSMED type B. This gene has likewise been implicated to be causative in an autosomal dominant OSMED (OSMED type A), fibrochondrogenesis-2, nonsyndromic DFNA13-associated autosomal dominant and DFNB53-associated autosomal recessive hearing loss.[4–6]

We describe a 2-year-old girl with phenotype and genotype suggestive of OSMED syndrome along with a literature review of patients reported with autosomal recessive OSMED (OSMED type B) syndrome harboring *COL11A2* pathogenic variants.

Clinical Phenotype and Genotype

A 2-year-old girl was referred to our clinic for genetic evaluation of short stature. She was from a Caucasian descent born out of a nonconsanguineous union. Polyhydramnios, breech presentation, and skeletal dysplasia detected by ultrasonography complicated the antenatal period and hence needed a cesarean section delivery. At birth, the proband weighed 3.6 kg (67th centile), measured 48.3 cm (34th centile) in length, and 35 cm (57th centile) as the head circumference. The proband was noted to have flat facies, mildly prominent eyes, flat nasal bridge, upturned nasal tip, posteriorly rotated ears, micrognathia, glossoptosis, complete cleft palate, short neck, short limbs, brachydactyly (two–five fingers), and sandal gap. There was no limitation of joint movements, and evidence of pectus and spine abnormalities on examination. The assessment of X-rays at birth showed poorly calcified vertebrae and vertebral bodies,

received
July 21, 2019
accepted after revision
September 3, 2019
published online
October 16, 2019

DOI https://doi.org/10.1055/s-0039-1698446.
ISSN 2146-4596.

short dumbbell femurs with metaphyseal flaring, short metacarpals, and phalanges. Also, the proband was found to have bilateral sensorineural hearing loss (SNHL) during the standard hearing screening at birth.

At 2 months of age, although the proband had short limbs with a bowed tibia and fibula, we observed that the features of skeletal dysplasia and dysmorphic features were less obvious compared with birth. Unfortunately, we were not able to present with the proband's photograph/X-rays with this report. The proband underwent palatoplasty for the correction of cleft palate and bilateral mandibular distraction using internal distraction devices for micrognathia, yet these devices were subsequently removed. The proband's developmental milestones were age appropriate, and no similar disease history was noted in her siblings or other family members.

Whole exome sequencing using available commercial methods in the proband revealed two heterozygous variants, c.190 C > T and c.339_340delCCinsG in exons 2 and 3 of *COL11A2*, respectively. Both the variants were novel, submitted to ClinVar database and confirmed by Sanger sequencing. Further, screening of both the parents via Sanger sequencing showed that they harbored one mutation each, supporting a transconfiguration and a compound heterozygous state in the proband. The c.339_340delCCinsG variant is predicted to result in a frameshift change, p.Leu114Trpfs*31 (ClinVar accession number: SCV000590729.2), while the c.190 C > T variant leads to a nonsense variant, p.Arg64* (ClinVar accession number: SCV000590451.3).

Discussion

COL11A2 (NM_080680.2; 6p21.32) encodes the α2(XI) collagen chain, a part of the heterotrimer including α1(XI) and α3 (XI) constituting the type XI collagen.[7] Type XI collagen is a cartilage-specific extracellular matrix (ECM) protein essential for cartilage collagen fibril formation, ECM organization, and necessary for the integrity and proper development of the skeleton.[1,8,9] Although quantitatively less significant compared with type II collagen, the type XI collagen is known to be expressed in various tissues such as the placenta, tendons, trabecular part of the bone, skeletal muscle, joint cartilage, testis, trachea, brain, inner ear, vitreous of the eye, and intervertebral discs. The type XI collagen also preserves the diameter and space between the fibrils of type II collagen, modulating fibrillogenesis.[10]

The phenotype of OSMED type B considerably overlaps with the genetically allelic autosomal dominant OSMED type A. OSMED type A, which is known previously as nonocular Stickler syndrome type 3 and WZS include a similar facial phenotype such as midface hypoplasia, anteverted nares, and micrognathia, cleft palate, SNHL, osteoarthritis, epiphyseal dysplasia, and absence of ocular defects.[1,11] To date, there is no adequate literature on OSMED to facilitate the clinical delineation between type A (autosomal dominant) and type B (autosomal recessive). Stickler spectrum of disorders and Kniest dysplasia are the other close differential diagnoses to consider in the evaluation of OSMED. It is established that both Kniest dysplasia and Stickler spectrum of disorders have similar facies, palatal cleft, SNHL, and skeletal findings as to the OSMED except for the presence of ocular defects such as high myopia cataracts and vitreoretinal abnormalities, enabling clinically differentiation prior to genetic tests.[12,13]

We reviewed the PubMed database with search terms "Otospondylomegaepiphyseal Dysplasia," "OSMED," "OSMED type B," "Weissenbacher–Zweymuller syndrome," "Autosomal Recessive Otospondylomegaepiphyseal Dysplasia," "Chondrodystrophy with sensorineural hearing loss," "Nance–Insley syndrome," and "Nance–Sweeney chondrodysplasia" to find out the previously reported OSMED patients with *COL11A2* pathogenic variants. Twenty-one cases with an OSMED phenotype have been published to harbor homozygous pathogenic variants in *COL11A2*. Certain findings such as midface hypoplasia, depressed nasal bridge, SNHL, and dysplastic skeletal changes were consistently present across all cases. Also, ocular defects such as high myopia, cataracts, retinal detachment, and vitreoretinal degeneration were absent in all cases (►**Table 1**), although few cases were noticed to have either slight myopia or hyperopia or strabismus.[2,14,15]

All the three differential diagnoses of OSMED discussed earlier are identified to be frequently caused by defects involving either type II or type IX collagen (Snead and Yates[12]; Vikkula et al[1]; Vuoristo et al[11]; and Wilkin et al[13]). While most of the OSMED type B cases are because of frameshift and nonsense variations in *COL11A2*, we do not have a hotspot locus for targeted sequencing and analysis (►**Fig. 1**). So far, only three groups have reported heterozygous pathogenic variants (two nonsense, one each in missense and in-frame deletion) in OSMED type A.[1,11,16] Until now, 14 pathogenic variants have been identified in 21 individuals diagnosed with OSMED type B. Of the 14 pathogenic variants, only one was a missense pathogenic variant, p.Gly661Arg on exon 27 of *COL11A2* (►**Fig. 1**). This pathogenic variant involving the triplet amino acid repeat Gly-X-Y in the collagen triple helical region has been proposed to affect the triple helix formation.[1,5] Three siblings reported to harbor this pathogenic variant were noted to have a slightly different phenotype with severe osteoarthritis that is not reported in other cases. This variation in the phenotype can be attributed to the functional effect of the missense pathogenic variant on the type XI collagen.[2,17]

Our proband presented with most of the features consistent with OSMED except for joint abnormalities such as enlarged joints or limited joint mobility, which were found in >80% of the described cases. She harbored two heterozygous variants inheriting one each from both parents. Both the variations, p.Arg64* and p.Leu114Trpfs*31, are located in the Lamin G-like domain and can be predicted to prematurely terminate or truncate the α2(XI) collagen chain before the collagen triple helical region (►**Fig. 1**). According to the American College of Medical Genetics and Genomics guidelines for variant classification, these variants can be classified as pathogenic.[18]

In conclusion, because of the frequency of OSMED type B cases, a diagnosis of OSMED type B over type A can be considered in patients with characteristic facies (midface hypoplasia, depressed nasal bridge, anteverted nares, micrognathia), SNHL,

Table 1 Comparison of clinical findings in OSMED type B across all clinical reports

Clinical findings	Our patient	Melkoniemi et al[2]	Tokgöz-Yilmaz et al[20]	Kayserili et al[19]	Harel et al[14] and Rabinowitz et al[15]	Temtamy et al[3]	van Steensel et al[17] and Vikkula et al[1]
Disproportionate, short limbs	+	10/10	+	2/2	4/4	2/2	2/3
Midface hypoplasia	+	10/10	+	2/2	NA	2/2	3/3
Anteverted nares	+	9/10	+	2/2	NA	2/2	3/3
Depressed nasal bridge	+	10/10	+	2/2	4/4	2/2	3/3
Micrognathia	+	7/10	+	2/2	4/4	1/2	NA
Cleft palate/ bifid uvula	+	10/10	–	1/2	4/4	0/2	0/3
Vertebral anomalies[a]	+	10/10	+	2/2	4/4	2/2	3/3
Radiograph abnormalities in pelvis and long bones[b]	+	6/10[c]	+	2/2	4/4	2/2	3/3
Limited joint mobility/ enlarged joints/ osteoarthritis	–	10/10	+	2/2	NA	0/2	3/3
Sensorineural hearing loss	+	10/10	+	2/2	4/4	2/2	3/3
Ocular defects (high myopia, vitreoretinal degeneration, retinal detachment, and cataracts)	–	0/10[d]	–	0/2	0/4[e]	0/2	0/3

Abbreviations: NA, not available; OSMED, otospondylomegaepiphyseal dysplasia; +/−, presence or absence of the finding in that reported case.
Note: The numbers in other cohorts indicate the number of patients having the clinical finding.
[a]Coronal clefts, platyspondyly, lumbar lordosis.
[b]Epiphyseal dysplasia, square iliac wings, dumbbell-shaped femurs, metaphyseal flaring.
[c]Radiograph details for 4 of 10 patients were not available.
[d]One patient had slight myopia.
[e]One patient had strabismus and four patients had hyperopia.

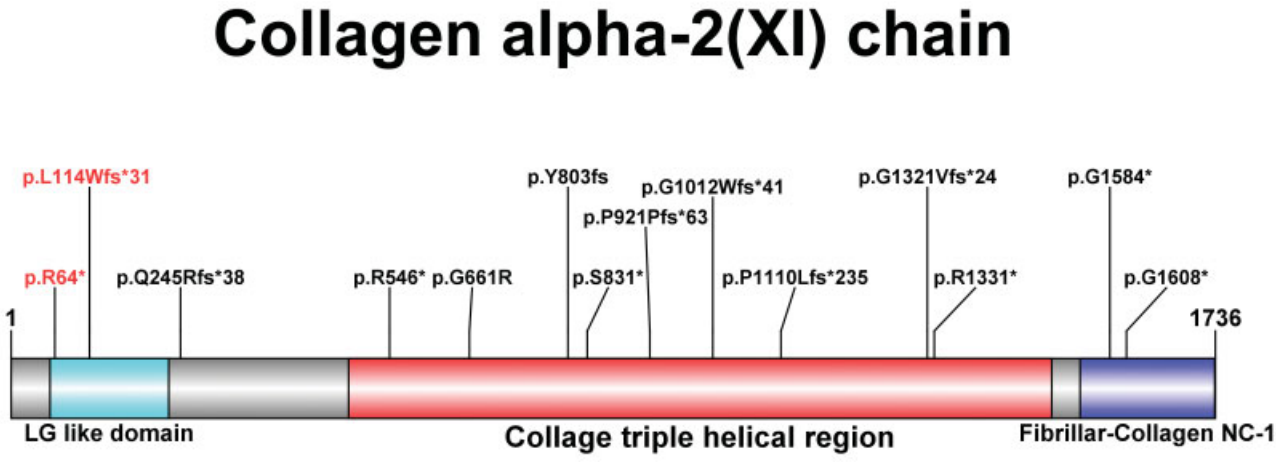

Fig. 1 Display of pathogenic variants on COL α-2(XI) chain. Black denotes the previously reported pathogenic variants.[2,3,14,17,19,20] Red denotes the pathogenic variants found in the proband. Splice defects (IVS22–2A > G, IVS53 + 5G > A) reported in Melkoniemi et al[2] are not displayed in the protein illustration. This figure was created using the software DOG (Domain Graph, version 1.0).[21] LG domain, Lamin G-like domain.

cleft palate, dysplastic skeletal changes (epiphyseal dysplasia, metaphyseal flaring, dumbbell-shaped femurs, vertebral clefts, platyspondyly), enlarged joints/limitation of joint mobility, and absence of ocular findings. Our case report adds to the expanding type XI collagen disease spectrum, enabling future genotype–phenotype correlation.

Note

ClinVar accession numbers are as follows:
Variant 1: c.339_340delCCinsG, p.Leu114Trpfs*31 (accession number: SCV000590729.2).
Variant 2: c.190 C > T, p.Arg64* (accession number: SCV000590451.3).

Funding
None.

Conflict of Interest
None declared.

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