Identification of three novel homozygous variants in **COL9A3** causing autosomal recessive Stickler syndrome

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**Abstract**

**Background:** Stickler syndrome (STL) is a rare, clinically and molecularly heterogeneous connective tissue disorder. Pathogenic variants occurring in a variety of genes cause STL, mainly inherited in an autosomal dominant fashion. Autosomal recessive STL is ultra-rare with only four families with biallelic **COL9A3** variants reported to date.

**Results:** Here, we report three unrelated families clinically diagnosed with STL carrying different novel biallelic loss of function variants in **COL9A3**. Further, we have collected **COL9A3** genotype–phenotype associations from the literature.

**Conclusion:** Our report substantially expands the molecular genetics and clinical basis of autosomal recessive STL and provides an overview about allelic **COL9A3** disorders.

**Keywords:** Autosomal recessive Stickler syndrome, **COL9A3**, Collagen, Hearing loss, Retinal detachment

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**Background**

Stickler syndrome (STL) is a rare, clinically and genetically heterogeneous connective tissue disorder divided into six clinical subtypes with overlapping features, including ocular pathologies (myopia, retinal detachment, vitreoretinal degeneration, cataract), hearing impairment (sensorineural, mixed, and/or conductive), craniofacial abnormalities (midface hypoplasia, anteverted nares, depressed nasal bridge and either Pierre Robin sequence or cleft palate and micrognathia) and joint problems (mild spondyloepiphyseal dysplasia, and precocious osteoarthritis) [1]. These features exhibit substantial variable expressivity according to clinical subtype [1]. STL is molecularly diagnosed by the presence of pathogenic variants in six collagen-type genes including **COL2A1**, **COL11A1**, **COL11A2**, **COL9A1**, **COL9A2**, **COL9A3**, and two non-collagen genes consisting of **LRP2** and **LOXL3** [1–3], following a predominantly autosomal dominant inheritance pattern.

The heteropolymer collagen XI/IX/II are critical in the extracellular matrix of joints, bones, ligaments and connective tissues throughout the body [4]. **COL2A1** encodes collagen type II alpha 1 chain. Heterozygous variants that cause functional haploinsufficiency are responsible for autosomal dominant STL type I (OMIM #108300), representing the most common subtype, accounting for roughly 80–90% of STL [5, 6]. Pathogenic variants in **COL11A1** cause the second most common STL subtype, type II (OMIM #604841) (10–20%). Variants in this gene likewise typically follow a dominant inheritance pattern [7], although five families have been described with STL and biallelic **COL11A1** mutations [8–10]. **COL11A2** pathogenic variants are very rare and cause...
autosomal dominant non-ocular Stickler syndrome (type III, OMIM#184840), also known as otopspondyloepiphyseal dysplasia (OSMEDA, OMIM# 120290), as well as Weissenbacher-Zweymuller syndrome (WZS) (OMIM #184840) [11]. Biallelic variants in \textit{LOXL3}, a member of the lysyl oxidase family of genes, have recently been causally associated with STL in two unrelated families [2, 12].

A biallelic missense variant in \textit{LRP2} has likewise been suggested to cause STL [3].

Collagen IX proteins are encoded by \textit{COL9A1}, \textit{COL9A2} and \textit{COL9A3} that together form fibril heterotrimer associated collagens and have been recently linked to autosomal recessive STL [13]. Very recently, heterozygous \textit{COL9A3} variants have been identified as causing peripheral vitreoretinal degeneration and retinal detachment [14]. \textit{COL9A1} and \textit{COL9A2} are causally associated with autosomal recessive STL type IV (OMIM #614134) and V (OMIM #61484), respectively. The main clinical characteristics of individuals affected with biallelic \textit{COL9A1} variants include moderate-to-severe sensorineural hearing loss, moderate-to-high myopia with vitreoretinopathy, and epiphyseal dysplasia, whereas \textit{COL9A2} variants are associated with high myopia, vitreoretinal degeneration, retinal detachment, hearing loss, and short stature. Only very recently, biallelic mutations in \textit{COL9A3} have been described to cause autosomal recessive STL in four unrelated families with seven patients. The main phenotypes that are common in all these patients consisted of high myopia, moderate to severe sensorineural hearing loss, and spondylo/epiphyseal dysplasia. Here, we report three additional unrelated consanguineous STL families with five affected individuals in total who each present three novel biallelic \textit{COL9A3} variants.

**Results**

**Clinical assessments**

Three unrelated consanguineous families of Iranian descent were referred for genetic testing due to hearing and vision impairment (Fig. 1), as well as skeletal dysplasia that resulted in a clinical diagnosis of STL (Fig. 2).

The female proband (III1) from Family 1 is the oldest and only affected individual out of three children from first cousin parents. She had a normal delivery and birth, with a birth weight of 3.2 kg (−0.43 SD). She was 28 years old at last examination with a weight of 64 kg (+0.41 SD), height of 157 cm (−0.8 SD) and occipitofrontal circumference (OFC) of 55 cm (+0.62 SD). She suffers from high myopia in both eyes, addition to vitreoretinal degeneration with empty vitreous, multiple lattice degenerations and retinal pigmentary changes. There was unilateral absence of the frontal sinus in her skull X-ray. She has severe and progressive sensorineural hearing loss. X-ray and detailed examination of her joints and bones, including mobility testing
and examination for signs of osteoarthritis were normal, however she complained of pain in her knee joints. Typical STL craniofacial features such as midface hypoplasia, cleft palate, micrognathia, depressed nasal bridge and anteverted nares are absent.

Family 2 presented with two affected individuals out of four children who were born from a first cousin marriage. The proband (II1) and his affected sibling (II2) both had a normal delivery around term, measurements at birth could not be obtained. Weight, height and OFC at last clinical assessment (at 65 and 57 years-old) were 68 kg (−0.16 SD) and 66 kg (−0.39 SD), 166 cm (−1.4 SD) and 163 cm (−1.8 SD), 56 cm (+0.62 SD) and 57 cm (+1.32 SD), respectively. Both had a history of multiple vitreoretinal surgeries due to recurrent rheumatogenous retinal detachments resulting from advanced vitreoretinal degeneration. Despite vitreoretinal surgeries, the older patient is considered blind without light perception (NLP) in either eye while his sibling has counting finger vision for one eye while NLP was noted for the other eye. Both suffer from severe and progressive sensorineural hearing loss. Likewise, both show a herniated cervical disc and muscular atrophy was noted in the older sibling. No radiologic documentation was available for review.

Family 3 presented with two affected and two healthy children from first cousin parents. Both affected individuals had normal delivery with a birth weight of 3.4 kg (−0.26 SD) and 3.75 kg (+0.71 SD), length of 49 cm (−0.6 SD) and 49.5 cm (0.1 SD), and OFC of 35 cm (−0.40 SD) and 36 cm (+0.62 SD). The most current weight, height and OFC measurements for the proband (II1) at age 11.8 years and his sister (II4) at age 3.1 years are 32 kg (−1.43 SD), 137 cm (0.9 SD), and 53 cm (+0.53 SD) and 12 kg (−0.05 SD), 84 cm (−0.6 SD), and 48 cm (−0.39 SD), respectively. Both affected individuals have myopia and congenital moderate to severe progressive sensorineural hearing impairment. The affected male complains of knee joint pain, especially when he runs. X-ray and detailed examination demonstrated spondyloepiphyseal dysplasia in both children. Both individuals...
Table 1  Summary of genetic and clinical findings in probands with biallelic \textit{COL9A3} variants

|                      | p.(Pro36Argfs*49)       | p.(Arg402*)            | p.(Arg402*)            | p.(Leu119Serfs*10)      | p.(Leu119Serfs*10)      | p.(Gln393Cysfs*25)       |
|----------------------|-------------------------|------------------------|------------------------|-------------------------|-------------------------|--------------------------|
|                      | Family 1                | Family 2, Patient 1    | Family 2, Patient 2    | Family 3, Patient 1     | Family 3, Patient 2     | Faletra et al. [15]      |
| Ethnicity            | Iranian                 | Iranian                | Iranian                | Iranian                 | Iranian                 | Moroccan                 |
| Consanguinity        | First cousin            | First cousin           | First cousin           | First cousin            | First cousin            | First cousin             |
| Sex                  | Female                  | Male                   | Male                   | Male                    | Female                  | Female                   |
| Age in years         | 28                      | 65                     | 57                     | 11 years, 8 months      | 3 years, 1 month        | 4                        |
| Birth                | Uncomplicated (normal delivery) | Uncomplicated (normal delivery) | Uncomplicated (normal delivery) | Uncomplicated (normal delivery) | Uncomplicated (normal delivery) | NA                       |
| Measurements         |                         |                        |                        |                         |                        |                          |
| OFC at last examination | 55 cm (+0.62 SD)  | 56 cm (+0.62 SD)       | 57 cm (+1.32 SD)       | 53 cm (−0.53 SD)         | 48 cm (+0.39 SD)         | NA                       |
| Weight at last evaluation | 64 kg (+0.41 SD)   | 68 kg (−0.16 SD)       | 66 kg (−0.39 SD)       | 32 kg (−1.43 SD)         | 12 kg (−0.05 SD)         | 16 kg                    |
| Height at last examination | 157 cm (−0.8 SD)  | 166 cm (−1.4 SD)       | 163 cm (−1.8 SD)       | 137 cm (0.9 SD)          | 84 cm (−0.6 SD)          | 107 cm                   |
| Myopia               | Moderate-to-high        | High                   | High                   | High                    | High                    | Moderate-to-high          |
| Vitreoretinal degeneration | No                    | Yes                    | Yes                    | No                      | No                      | No                       |
| Cataract             | No                      | Yes                    | Yes                    | No                      | No                      | No                       |
| Retinal detachment   | No                      | Yes                    | Yes                    | No                      | No                      | No                       |
| Auditory system      |                         |                        |                        |                         |                         |                          |
| Hearing loss         | Yes                     | Yes                    | Yes                    | Yes                     | Yes                     | Yes                      |
| Age at onset         | NA                      | NA                     | NA                     | Early onset             | Early onset             | Early onset              |
| Type                 | Sensorineural           | Sensorineural          | Sensorineural          | Sensorineural           | Sensorineural           | Sensorineural             |
| Degree of hearing loss | Severe                 | Profound               | Profound               | Moderate-to-severe      | Moderate-to-severe      | Moderate-to-severe        |
| Progressive/stable   | Progressive             | Progressive            | Progressive            | Progressive             | Progressive             | Progressive              |
| Joints               |                         |                        |                        |                         |                         |                          |
| Short stature        | No                      | No                     | No                     | No                      | No                      | No                       |
| Spondyloepiphyseal dysplasia | No     | No                     | No                     | Yes                     | Yes                     | Yes                      |
| Epiphyseal dysplasia | No                      | No                     | No                     | Yes                     | Yes                     | Yes                      |
| Craniofacial structures | No                   | No                     | No                     | No                      | No                      | No                       |
| Midface hypoplasia   | No                      | No                     | No                     | No                      | Yes                     | Yes                      |
| Cleft palate         | No                      | No                     | No                     | No                      | No                      | No                       |

|                      | p.(Gln393Cysfs*25)     | p.(Gln393Cysfs*25)     | p.(Pro218Alafs*49)     | p.(Arg471Ter)           | p.(Arg471Ter)           | p.(Arg90Ter) and p.(Arg577Ter) |
|----------------------|------------------------|------------------------|------------------------|-------------------------|-------------------------|-----------------------------|
|                      | Faletta et al. [15]    | Faletta et al. [15]    | Hanson-Kahn et al. [16]| Nixon et al. [13]        | Nixon et al. [13]        | Markova et al. [19]         |
| Ethnicity            | Moroccan               | Moroccan               | Indian                 | NA                      | NA                      | Russian                     |
| Consanguinity        | First cousin           | First cousin           | Third cousin           | NA                      | NA                      | No                          |
| Sex                  | Male                   | Male                   | Male                   | NA                      | NA                      | Male                        |
| Age in years         | 11                     | 16                     | 12                     | 18                      | 20                      | At term                     |
| Birth                | NA                     | NA                     | Uncomplicated (Caesarean section) | NA                      | NA                      | NA                          |
| Measurements         |                         |                        |                        |                         |                         |                             |
| OFC at last examination | NA                   | NA                     | NA                     | NA                      | NA                      | NA                          |
| Weight at last evaluation | 38 kg                 | 60 kg                  | NA                     | NA                      | NA                      | 13 kg (50th %ile)           |
II1 and II4 have pes planus, depressed nasal bridge and anteverted nares, with midface hypoplasia and downslanting palpebral fissures more pronounced in II4. Detailed clinical features of all affected individuals are described in Table 1 and Additional file 1: Table S1. None of the individuals showed signs of intellectual disability.

**Genetic analysis**

The DNA of probands from the three unrelated families (family 1 proband II1, family 2 proband II1, family 3 proband II1) was subjected to Exome Sequencing (ES), revealing three different novel, homozygous loss of function (LOF) variants in COL9A3, NM_001853.3. The proband in Family 1 was found to have a COL9A3 deletion (c.107_116del, p.(Pro36Argfs*49), rs1470627424), causing a frameshift in exon 2. The allele frequency in gnomAD is 0.00001390 with two carriers, while other public genomic databases such as Iranome and GME, and 1000 genomes have not reported this variant. The proband in family 2 disclosed a COL9A3 nonsense variant (c.1204C > T, p.(Arg402*), rs989413835) in exon 23, while the proband in Family 3 showed a one base pair deletion in COL9A3 [c.355delC, p.(Leu119Serfs*9)] in exon 7. Both variants have not been reported in public databases.

**Discussion**

Here, we report three families with five affected individuals clinically diagnosed with autosomal recessive STL due to biallelic LOF variants in COL9A3. Our report reaffirms previous studies that have described four families with biallelic LOF causing autosomal recessive STL, increasing the total number of families reported to date to seven [13, 15, 16]. These COL9A3 variants as well as other disease causing COL9A3 variants submitted to HGMD are visualized in Fig. 3 for localization on cDNA as well as on protein level.

**Table 1**  (continued)

| Phenotype | Family 1 Patient 2 | Family 2 Patient 3 | Family 3 Patient 1 | Family 1 Patient 2 | Family 2 Patient 3 | Family 3 Patient 1 |
|-----------|--------------------|--------------------|--------------------|--------------------|--------------------|--------------------|
| Height at last examination | 144 cm | 170 cm | NA | NA | NA | 88 cm (25–50th %ile) |
| Myopia | Moderate-to-high | Moderate-to-high | High | High | High | High |
| Vitreoretinal degeneration | No | No | No | No | No | No |
| Cataract | No | No | No | No | No | No |
| Retinal detachment | No | No | No | No | No | No |
| Auditory system | | | | | | |
| Hearing loss | Yes | Yes | Yes | Yes | Yes | Yes |
| Age at onset | NA | NA | Early onset | NA | NA | Yes |
| Type | Sensorineural | Sensorineural | Sensorineural | Sensorineural | Sensorineural | Sensorineural |
| Degree of hearing loss | Moderate-to-severe | Moderate-to-severe | Moderate-to-severe | Moderate-to-severe | Moderate-to-severe | Moderate-to-severe |
| Progressive/stable | Progressive | Progressive | Stable | Progressive | Progressive | NA |
| Joints | | | | | | |
| Short stature | No | No | No | No | No | No |
| Spondyloepiphyseal dysplasia | No | No | No | No | No | Yes |
| Epiphyseal dysplasia | Yes | Yes | Yes | Yes | NA | NA |
| Craniofacial structures | | | | | | |
| Midface hypoplasia | Yes | Yes | Yes | No | No | Yes |
| Cleft palate | No | No | No | No | No | No |

NA not ascertained, OFC occipitofrontal circumference, SD standard deviation
different members of collagen IX have supported the hypothesis that each of the three proteins is essential for collagen IX function [13, 18].

While a variety of disorders have been described to result from heterozygous pathogenic variants in \( \text{COL9A3} \), only four unrelated STL families and one family with nonsyndromic hearing loss have been reported to date carrying biallelic variants (Table 2). Allelic disorders resulting from \( \text{COL9A3} \) variants include nonsyndromic hearing loss, MED, pseudoachondroplasia, cerebral palsy, and lumbar disc disease and severe peripheral vitreoretinal degeneration and retinal detachment (Table 2).

Consistent clinical features among STL patients with biallelic \( \text{COL9A3} \) LOF alleles comprise moderate-to-profound progressive sensorineural hearing loss and moderate high myopia with vitreoretinal degeneration. Retinal detachment and cataract occur occasionally. In contrast, skeletal involvement seems to be more variable. For instance, Nixon et al. [13] reported a family with two affected siblings where the oldest affected sibling had severe arthropathy in the shoulders and hip, requiring a wheelchair. The X-ray of this patient showed spinal scoliosis and narrowing of the articular space in both knees, while the younger affected sibling did not show any of these signs. In line with this report, we also observed that the affected individuals in family 2, at the ages of 65 and 57 years-old, suffer only from myopia, hearing loss and each have a herniated cervical disc while the two much younger affected individuals in family 3, at ages 3 and 11 years-old, have more prominent skeletal findings that include radiological signs of spondyloepiphyseal dysplasia as well as craniofacial abnormalities including depressed nasal bridge and anteverted nares (Table 1). Moreover, Nixon et al. [13] observed that carrier parents
Table 2  Pathogenic COL9A3 variants reported in HGMD and associated clinical phenotypes

| c.DNA position | Protein position | Exon/intron | Description | Zygosity | dbSNP   | ClinVar     | Reported phenotype                                      | References                  |
|----------------|------------------|-------------|-------------|-----------|---------|-------------|---------------------------------------------------------|------------------------------|
|                 |                  |             | 99 bp duplication (CNV) | Het       | NA      | NA          | Sensorineural hearing loss                               | Ji (2014) BMC Ear Nose Throat Disord 14,9 |
| c.97C>T        | p.(Pro33Ser)     | 2           | Missense    | Het       | rs745914662 | NA          | Cerebral palsy                                          | Pingel (2019) Am J Med Genet B Neuropsychiatr Genet 180,12 |
| c.104G>A       | p.(Gly35Asp)     | 2           | Missense    | Het       | rs1390736361 | NA          | Multiple epiphyseal dysplasia                           | Jeong (2014) BMC Musculoskelet Disord 15,371 |
| c.148-1G>A     | p.?              | 2           | Splicing    | Het       | rs606231367 | NA          | Multiple epiphyseal dysplasia                           | Lohiniva (2000) Am J Med Genet 90,216 |
| c.148-2A>G     | p.?              | 2           | Splicing    | Het       | NA       | NA          | Multiple epiphyseal dysplasia                           | Jackson (2012) Hum Mutat 33,144 |
| c.148-2A>T     | p.?              | 2           | Splicing    | Het       | NA       | P           | Multiple epiphyseal dysplasia                           | Paasilita (1999) Am J Hum Genet 64,1036 |
| c.183+5G>A     | p.?              | 3           | Splicing    | Het       | NA       | P           | Multiple epiphyseal dysplasia                           | Nakashima (2005) Am J Med Genet 132A,181 |
| c.268C>T       | p.(Arg90Ter)     | 5           | Nonsense    | Comp het  | rs763259234 | NA          | Stickler syndrome                                      | Markova (2021) Mol Genet Genomic Med |
| c.369+2T>C     | p.?              | 7           | Splicing    | Het       | rs1057518693 | P           | Multiple epiphyseal dysplasia                           | Posey (2017) N Engl J Med 376,21 |
| c.369+8C>G     | p.?              | 7           | Splicing    | Het       | NA       | NA          | Severe peripheral vitreoretinal degeneration and retinal detachment | Lord (2019) Genome Res 29,159 |
| c.388G>A       | p.(Gly130Ser)    | 8           | Missense    | Het       | rs139401633 | VUS         | Multiple epiphyseal dysplasia                           | M. Nash (2021) European Journal of Human Genetics |
| c.543_551del   | p.(Pro185_ Gly187del) | 11       | In frame   | Hom       | rs765392378 | NA          | Nonsyndromic hearing loss                               | Asamura (2005) Auris Nasus Larynx 32,113 |
| c.650dupC      | p.(Gly217Trpfs*50) | 13       | Frameshift  | Hom       | NA       | NA          | Nonsyndromic hearing loss                               | Hanson-Kahn (2018) Am J Med Genet A 176,2887 |
| c.971A>T       | p.(Asn324Ile)    | 19          | Missense    | Het       | NA       | NA          | Pseudoachondroplasia                                    | Jung (2010) Int J Mol Med 26,885 |
| c.1107+1G>C    | p.?              | 21          | Splicing    | Het       | NA       | NA          | Severe peripheral vitreoretinal degeneration and retinal detachment | M. Nash (2021) European Journal of Human Genetics |
| c.1176_1198del | p. (Gln393Cyster*25) | 23       | Frameshift  | Hom       | rs606231470 | VUS         | Stickerl syndrome                                       | Faletra (2014) Am J Med Genet A 164,42 |
| c.1277>T>C     | p.(Val426Ala)    | 24          | Missense    | Het       | NA       | NA          | Pseudoachondroplasia                                    | Jung (2010) Int J Mol Med 26,885 |
| c.1361G>A      | p.(Gly454Glu)    | 26          | Missense    | Het       | NA       | NA          | Nonsyndromic hearing loss                               | Miyagawa (2013) PLoS One 8,e71381 |
| c.1411T>C      | p.(Arg471ter)    | 28          | Nonsense    | Hom       | rs747896279 | P           | Stickerl syndrome                                       | Nixon (2019) Am J Med Genet A 179,1498 |
| c.1649C>T      | p.(Pro550Leu)    | 30          | Missense    | Het       | rs535230112 | NA          | Nonsyndromic hearing loss                               | Miyagawa (2013) PLoS One 8,e71381 |
| c.1729C>T      | p.(Arg577Ter)    | 30          | Nonsense    | Comp het  | rs1201247953 | NA          | Stickerl syndrome                                       | Markova (2021) Mol Genet Genomic Med |
| c.1851C>A      | p.(Asp617Glu)    | 31          | Missense    | Het       | rs199577452 | NA          | Nonsyndromic hearing loss                               | Asamura N Auris Nasus Larynx 32,113 |

All variants are reported using the NM_001853.3 transcript

Comp het compound heterozygous, Het heterozygous, Hom homozygous, P pathogenic, VUS variant of uncertain significance, NA not ascertained
can manifest mild STL phenotypes, while our report and others [15, 16, 19] have not observed mild phenotypes in heterozygous individuals. Besides Nixon’s report, Markova et al. [19] introduced a more severe case with compound heterozygous variants with vitreoretinal degeneration, early onset osteoarthritis, midface hypoplasia, hip dysplasia, speech developmental delay, spina bifida, kyphosis, and eye pigment rearrangement.

Conclusion
In summary, our report consolidates that homozygous loss of function variants in \textit{COL9A3} cause STL (type VI). We find high myopia and moderate-severe hearing loss to be consistent features amongst all cases while skeletal findings seem more variable.

Material and methods
Subjects
Three unrelated Iranian families with syndromic phenotypes including hearing loss, vision impairment and skeletal dysplasia were referred for clinical genetic diagnostics. Blood samples were collected after obtaining informed consent from patients or their parents. Molecular genetic diagnostic testing was performed in Nijmegen via the Radboud innovative diagnostics programme and at the University of Tuebingen (197/2019BO01). Informed consent from the parents or legal guardians of the patients/participants was obtained for the publication of their data.

Exome and Sanger sequencing
After extraction of DNAs from whole blood by standard protocol, proband DNA samples were subjected to exome capture using the Agilent SureSelect Human All Exon V6 Kit and exome sequencing (ES) was performed on an Illumina HiSeq 2500 sequencer for an average $50 \times$ sequencing depth, resulting in sequences of greater than 100 bases from each end of the fragments [Cambridge (Novogene UK)]. Exome data were processed for analysis using a GATK-based pipeline [20] that uses Burrows-Wheeler alignment [21] to the GRCh37/UCSC hg19 (Families 1 and 2) and GRCh38/UCSC hg38 (Family 3). VarScan version 2.2.5, MuTec and GATK Somatic Indel Detector were used to detect SNV and InDels, respectively. The protocol to interpret potential pathogenic variants was previously described [22]. For population-specific filtering, gnomAD [23], Iranome [24] and Greater Middle East (GME) Variome Project [25] databases were used.

Segregation analysis using Sanger sequencing was performed in available family members to confirm variant segregation after PCR amplification. Primers are available upon request.

Web resources
ClinVar, https://www.ncbi.nlm.nih.gov/clinvar/
Exome Aggregation Consortium (ExAC), http://exac.broadinstitute.org.
Genome Aggregation Database (gnomAD), http://gnomad.broadinstitute.org/

Abbreviations
DNA: Deoxyribonucleic acid; ES: Exome sequencing; FACIT: Fibril-associated collagen with interrupted triple helicities; GATK: Genome Analysis Toolkit; GME: Greater Middle East; LOF: Loss of function; MED: Multiple Epiphyseal Dysplasia; OFC: Occipitofrontal circumference; PCR: Polymerase Chain Reaction; SD: Standard deviation; SNV: Single Nucleotide Variant; STL: Stickler syndrome.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s13023-022-02244-6.

Additional file 1. Table S1: Clinical features of probands affected by COL9A3 variants.

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Authors’ contributions
FS, RM, EGK, ND, MD, AM, HA, HS, MR and NH recruited the probands and/or were involved in their clinical care. AR, MN, SL and DM conducted genetic data analysis. AR, MN, BV and MS conceived the study. AR, MN, BV and MS drafted the manuscript. BV and MS supervised the study. All authors read and approved the final version of the manuscript.

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Availability of data and materials
Data can be made available on personal request. Variants reported in this study have been deposited in the Leiden Open Variation Database (LOVD) and are available through the following variant accession numbers: 0000364418, 0000364419 and 0000364420.

Declarations
Ethics approval and consent to participate
Molecular genetic diagnostic testing was performed in Nijmegen via the Radboud innovative diagnostics programme and at the University of Tuebingen (197/2019BO01).

Consent for publication
Informed consent from the parents or legal guardians of the patients/participants was obtained for the publication of their data.
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