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Type II Collagen Disorders Overview

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Summary

The purpose of this *GeneReview* is to:

1. Describe the clinical characteristics of type II collagen disorders;
2. Provide an evaluation strategy to identify the genetic cause of a type II collagen disorder in a proband;
3. Review the differential diagnosis of type II collagen disorders with a focus on genetic conditions;
4. Review management of type II collagen disorders;
5. Inform genetic counseling of family members of an individual with a type II collagen disorder.

1. Clinical Characteristics of Type II Collagen Disorders

Clinical Description

Type II collagen is an essential component of the cartilage extracellular matrix, and of major importance in endochondral bone formation, growth, and normal joint function. It is also necessary for normal development and function of the eye and the inner ear. Type II collagen disorders encompass a diverse group of clinical phenotypes characterized by skeletal dysplasia, ocular manifestations (e.g., cataract, myopia, subluxation of the lens, vitreous abnormalities, retinal detachment), hearing impairment, and orofacial features [Nishimura et al 2005, Kannu et al 2012, Spranger et al 2012a, Terhal et al 2015, Savarirayan et al 2019].

The spectrum of severity ranges from severe perinatal-lethal disorders to milder conditions presenting in adulthood with premature arthrosis as the primary feature. Considerable phenotypic overlap notwithstanding, discriminating features can aid in the specific diagnosis (see Table 1). The following individual phenotypes are recognized in the 2023 revision of the Nosology of Genetic Skeletal Disorders [Unger et al 2023], and can be grouped according to severity.

Most severe (often lethal perinatally)

- Achondrogenesis, *COL2A1*-related (formerly type II, type Langer-Saldino)

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- Hypochondrogenesis, *COL2A1*-related
- Platyspondylic dysplasia, type Torrance, *COL2A1*-related

Severe / moderately severe (neonatal presentation)

- Kniest dysplasia, *COL2A1*-related
- Spondyloepiphyseal dysplasia congenita (SEDC), *COL2A1*-related
- Spondyloepimetaphyseal dysplasia (SEMD), *COL2A1*-related

Intermediate (neonatal/childhood/adolescent presentation)

- Spondyloperipheral dysplasia, *COL2A1*-related
- Spondyloepiphyseal dysplasia (SED) with metatarsal shortening, *COL2A1*-related
- Stickler syndrome, *COL2A1*-related

Mild (adolescent/adult presentation)

- Mild spondyloepiphyseal dysplasia (SED) with premature arthrosis

Most Severe (often lethal perinatally)

Achondrogenesis, *COL2A1*-related, is the most severe type II collagen disorder. Achondrogenesis, *COL2A1*-related, usually presents in the prenatal setting with short stature, extremely short limbs (micromelia), narrow chest with pulmonary hypoplasia, extraskeletal features (e.g., flat midface, Pierre Robin sequence [PRS]), and edema/hydropic appearance. Radiographic findings include poor ossification of the axial skeleton, absent or delayed ossification of the vertebral bodies, absent ossification of the sacrum, and absent or severely delayed ossification of pubic and ischial bones. Iliac bones are small with crescent-shaped inner and inferior margins. The distal femora and proximal tibiae show delayed ossification, and the ribs and tubular bones are short. The majority of these infants do not survive to term, and are often delivered prematurely, are stillborn, or die shortly after birth as a result of cardiorespiratory failure [Spranger et al 2012b].

Hypochondrogenesis, *COL2A1*-related, is characterized by short limbs, small thorax, flat facial profile, PRS, and delayed skeletal ossification, but with less severe clinical course and skeletal involvement than achondrogenesis, *COL2A1*-related. Vertebral bodies are small and ovoid, and unossified in the cervical region. The pubic bones are unossified and the ilia are hypoplastic. There is shortening of the long bones and delayed ossification in distal femoral and proximal tibial epiphyseal ossification centers. Infants with hypochondrogenesis have a short survival span ranging from days to months [Castori et al 2006].

Note: Achondrogenesis, *COL2A1*-related, and hypochondrogenesis, *COL2A1*-related, form one phenotypic continuum.

Platyspondylic dysplasia, type Torrance, *COL2A1*-related, is characterized by disproportionate short stature, short limbs, and coarse facial features. Skeletal findings consist of very thin vertebral bodies (severe platyspondyly), incomplete vertebral ossification, short ribs and narrow chest, short long bones with delayed/poor ossification, and splayed metaphyses of ribs and long bones. The majority of infants die at or shortly after birth; however, individuals with long-term survival have been reported [Nishimura et al 2004, Spranger et al 2012e, Handa et al 2021].

Severe / Moderately Severe (neonatal presentation)

Kniest dysplasia, *COL2A1*-related, is a very severe type II collagen disorder, but results in live birth and longer survival. The clinical presentation is characterized by severe disproportionate short stature, short neck, short thorax, short extremities, and distinct ocular findings: myopia, vitreal abnormalities, and retinal detachment. Radiographically, Kniest dysplasia, *COL2A1*-related, presents with pronounced abnormalities of bone modeling

including platyspondyly with anterior wedging and coronal clefting of the lumbar vertebral bodies, delayed ossification in distal femoral and proximal tibial epiphyseal ossification centers, and short long bones with large metaphyses and epiphyses (dumbbell-type deformity of the long bones). Significant medical complications can occur mainly as a result of hypoplasia of the dens leading to cervical instability and spinal cord compression, tracheolaryngomalacia and related respiratory complications, and early-onset arthrosis [Yazici et al 2010, Spranger et al 2012c, Sergouniotis et al 2015, Handa et al 2021].

Spondyloepiphyseal dysplasia congenita (SEDC), *COL2A1*-related. Individuals with SEDC, *COL2A1*-related, present neonatally with severe disproportionate short stature, short extremities (<5th centile), characteristic facial features (hypertelorism, flat profile, PRS), myopia, and hearing loss. Radiographs display delayed/poor ossification of the vertebrae and the pubic bones, and the long bones are short with hypoplastic epiphyses. There is an increased risk for cervical instability and spinal cord compression (as seen in Kniest dysplasia, *COL2A1*-related), and individuals with SEDC, *COL2A1*-related, are also at greater risk for tracheolaryngomalacia and related respiratory complications.

SEDC, *COL2A1*-related, cannot be distinguished from spondyloepimetaphyseal dysplasia, *COL2A1*-related, until later in the first year of life, since metaphyseal dysplasia in the latter is not present at birth [Spranger et al 2012d, Terhal et al 2015].

Spondyloepimetaphyseal dysplasia (SEMD), *COL2A1*-related. Infants with SEMD, *COL2A1*-related, initially present with the same clinical and radiographic findings as those with SEDC, *COL2A1*-related. However, within the first year of life, metaphyseal flaring becomes evident, suggesting the diagnosis of SEMD, *COL2A1*-related. The clinical course is similar to that of SEDC, *COL2A1*-related, with increased risk for cervical instability and spinal cord compression posing the greatest risk for these individuals [Walter et al 2007, Terhal et al 2015, Handa et al 2021].

Intermediate (neonatal/childhood/adolescent presentation)

Spondyloperipheral dysplasia, *COL2A1*-related, is characterized by mild-to-moderate disproportionate short stature and short extremities, brachydactyly type E, short ulnae, variable clubfeet, cleft palate, myopia, and hearing loss. Radiographs show ovoid vertebra, delayed ossification of pubic bones, and flattened and irregular epiphyses in the long bones in addition to the brachydactyly and short ulnae. Premature hip arthrosis causes joint pain [Zankl et al 2004, Handa et al 2021].

Spondyloepiphyseal dysplasia (SED) with metatarsal shortening, *COL2A1*-related, is characterized by severe joint pain in the lower limbs before adolescence and shortening of the postaxial toes (usually the 3rd and/or 4th toes). Height is average, and ocular and orofacial abnormalities are absent. Radiographs are characterized by mild platyspondyly with irregular end plates, narrowed intervertebral spaces, signs of osteoarthrosis including deformed femoral heads and dysplastic pelvis with irregular acetabulae, and shortening of the metatarsal and metacarpal bones [Kozlowski et al 2004, Marik et al 2004, Hoornaert et al 2007, Handa et al 2021].

Stickler syndrome, *COL2A1*-related, is one of the milder and more frequent type II collagen disorders [Barat-Houari et al 2016b, Barat-Houari et al 2016c], and the most common type of Stickler syndrome. It shows remarkable inter- and intrafamilial phenotypic variation, with severity ranging from involvement of many organs to milder phenotypes with only ocular manifestations and clinical and radiographic findings of early-onset osteoarthrosis. The ocular manifestations include high myopia, congenital membranous vitreous abnormalities (most often type 1 congenital vitreous anomaly or "membranous" vitreous phenotype), retinal detachment, and early-onset cataract. The orofacial abnormalities include flat facial profile (underdevelopment of the maxilla and nasal bridge), isolated small jaw, isolated cleft palate, or a combination (PRS), and hearing loss that can be conductive and/or sensorineural. The musculoskeletal manifestations include mild short stature or average stature, joint hypermobility, and skeletal dysplasia. Radiographic features include mild-to-moderate flattening of the vertebra with or without end plate irregularities, and irregular epiphyses of the long bones

[Szymko-Bennett et al 2001, Liberfarb et al 2003, Rose et al 2005, Snead et al 2011, Acke et al 2012]. Typically, phenotypic findings present in childhood or later, although micrognathia, cleft palate, and polyhydramnios have been detected on prenatal ultrasound [Soulier et al 2002, Pacella et al 2010, Handa et al 2021].

Mild (adolescent/adult presentation)

Mild spondyloepiphyseal dysplasia (SED) with premature-onset arthrosis is the mildest form of type II collagen disorder. It is characterized clinically by progressive joint pain and limitation of motion of the hip and knee joints, and radiographically by epiphyseal dysplasia and early-onset osteoarthrosis. The manifestations are age dependent, and height, vision, hearing, and orofacial structures are usually normal [Su et al 2008, Kannu et al 2010, Kannu et al 2011, Handa et al 2021]. In the 2023 revision of the Nosology of Genetic Skeletal Disorders [Unger et al 2023], mild SED with premature-onset arthrosis is included under SEDC, *COL2A1*-related.

Table 1. Clinical and Radiographic Features of Type II Collagen Disorders from Most to Least Severe

COL2A1-Related Disorder	Age of Diagnosis	Poor/ Delayed Ossification	Stature	Extraskeletal Abnormalities	Distinguishing Feature(s) [1]	
					Clinical	Radiographic
Most severe (often lethal perinatally) [2]						
Achondrogenesis	Prenatal	++++++	Extremely short	Flat midface; PRS; hydropic appearance	Often delivered prematurely, stillborn, or die shortly after birth (hrs)	Absent or severely delayed ossification of vertebral bodies; short ribs; absent ossification of pubic bones, sacrum, & ischial & iliac bones (small w/crescent-shaped inner & inferior margins); very short tubular bones w/delayed ossification in distal femoral & proximal tibial epiphyseal ossification centers
Hypochondrogenesis	Prenatal	+++++	Extremely short	Flat midface; PRS	Majority alive at birth, short survival (days to mos)	Poor/delayed ossification of axial skeleton; very short tubular bones in prenatal period; short ribs; vertebral bodies are small & ovoid, & unossified in cervical region; unossified pubic bones; hypoplastic ilia; short & relatively broad long bones w/ delayed ossification in distal femoral & proximal tibial epiphysis

Table 1. continued from previous page.

COL2A1-Related Disorder	Age of Diagnosis	Poor/ Delayed Ossification	Stature	Extraskeletal Abnormalities	Distinguishing Feature(s) [1]	
					Clinical	Radiographic
Platyspondylic dysplasia, type Torrance	Prenatal	+++++	Extremely short	Coarse facial features	Majority alive at birth, short survival (days to mos)	Platyspondyly; incomplete vertebral ossification; short ribs & narrow chest; splayed metaphyses of ribs & long bones
Severe to moderately severe (neonatal presentation)						
Kniest dysplasia	Perinatal	++++	Short	PRS; high prevalence of myopia, lens subluxation, retinal detachment, & other vitreal abnormalities; ↑ risk of tracheolaryngomalacia	Most severe type II collagen disorder resulting in live birth; long-term joint problems; risk of cervical instability & myelopathy	Platyspondyly w/ anterior wedging in low thoracic & lumbar region; coronal cleft vertebral bodies; delayed ossification in distal femoral & proximal tibial epiphyseal ossification centers; dumbbell-type deformity of long bones (large metaphyses & epiphyses)
SEDC	Perinatal	+++	Short	Flat facial profile, hypertelorism, PRS; ocular abnormalities; ↑ risk of tracheolaryngomalacia	Severe disproportionate short stature/ extremities (˂5th %ile); ↑ risk of cervical instability & spinal cord compression	Delayed/absent ossification of pubic bones, spine, & distal femoral & proximal tibial epiphyseal ossification centers; delayed carpal & tarsal ossification
SEMD	Perinatal	+++	Short			Delayed ossification of pubic bones, spine, & distal femoral & proximal tibial epiphyseal ossification centers; metaphyseal dysplasia in 1st year of life (distinguishing SEMD, Strudwick type, from SEDC)
Intermediate (neonatal/childhood/adolescent presentation)						

Table 1. continued from previous page.

COL2A1-Related Disorder	Age of Diagnosis	Poor/ Delayed Ossification	Stature	Extraskeletal Abnormalities	Distinguishing Feature(s) [1]	
					Clinical	Radiographic
Spondyloperipheral dysplasia	Perinatal/ infancy	++	Short	Myopia; hearing loss	Moderate-to-mild disproportionate short stature; short extremities; brachydactyly; occasionally clubfeet	Ovoid vertebra & irregular epiphyses in long bones; brachydactyly type E; short ulnae
SED w/metatarsal shortening	Before adolescence	Normal	Average	Usually no extraskeletal abnormalities	Typical phenotypic hallmark: shortening of 3rd & 4th toes; severe joint pain	Platyspondyly w/ irregular end plates; narrowed intervertebral spaces; early osteoarthrosis in spine & lower limb joints (deformed femoral heads & dysplastic pelvis); metatarsal hypoplasia involving postaxial toes
Stickler syndrome	Variable (typically perinatal if cleft palate)	Normal	Mild short to average	High risk of high myopia, congenital membranous vitreous abnormalities, retinal detachment, & cataract; U-shaped cleft palate; auditory manifestations	In case of PRS, diagnosis most often in infancy	Radiographic appearance of precocious or inflammatory arthritis (childhood)
Mild (adolescent/adult presentation)						
Mild SED w/ premature-onset arthrosis	Adolescence/ adulthood	Normal	Average	Vision, hearing, & orofacial structures are usually normal.	Progressive joint pain & limitation of motion of hip & knee joint	Epiphyseal dysplasia & early-onset osteoarthrosis

PRS = Pierre Robin sequence; SED = spondyloepiphyseal dysplasia; SEDC = spondyloepiphyseal dysplasia congenita; SEMD = spondyloepimetaphyseal dysplasia

1. Features distinguishing this disorder from other type II collagen disorders

2. Can be very difficult to distinguish prenatally

Genotype-Phenotype Correlations

There is currently no clear genotype-phenotype correlation in type II collagen disorders, and there is significant phenotypic overlap. However, data do support some general rules [Nishimura et al 2005, Hoornaert et al 2006, Terhal et al 2015, Barat-Houari et al 2016b, Barat-Houari et al 2016c] (see also Leiden Open Variation Database [LOVD]). Most pathogenic *COL2A1* variants involve the triple helix domain.

- Missense variants in the Gly position of the Gly-X-Y repeat motif cause substitution of glycine to a bulkier amino acid, interfering with triple helix formation. This dominant-negative effect is generally seen in the more severe *COL2A1*-related disorders (e.g., achondrogenesis; platyspondylic dysplasia, type Torrance; SEDC; and SEMD).

- In Kniest dysplasia, *COL2A1*-related, exon skipping is more common [Barat-Houari et al 2016b, Barat-Houari et al 2016c], and it appears that splicing variants impose a higher risk for ophthalmologic complications and hearing loss [Terhal et al 2015].
- Arginine-to-cysteine substitutions are most often associated with non-lethal phenotypes [Hoornaert et al 2006]. A p.Arg275Cys substitution in the Y position of the Gly-X-Y repeat motif causes SED with metatarsal shortening, *COL2A1*-related [Hoornaert et al 2007].
- In Stickler syndrome, *COL2A1*-related, nonsense and frameshift variants dominate, introducing a premature termination codon leading to haploinsufficiency [Richards et al 2006].

Penetrance

Penetrance in type II collagen disorders is high, if not complete; only rare instances of apparently reduced penetrance have been reported [Barat-Houari et al 2016b]. However, the milder disorders have age-dependent phenotypic manifestations, and wide inter- and intrafamilial phenotypic variation has been reported [Liberfarb et al 2003, Nakashima et al 2016]. At present, knowledge of underlying mechanisms is limited, but the phenotypic variation is likely caused by environmental factors and polymorphisms in disease-modifying genes and/or regulatory elements [Bell et al 1997, Bi et al 1999, Liberfarb et al 2003, Kannu et al 2010, Nakashima et al 2016, Yasuda et al 2017].

Nomenclature

Achondrogenesis, *COL2A1*-related, was formerly known as achondrogenesis type II or achondrogenesis, type Langer-Saldino.

SED with metatarsal shortening, *COL2A1*-related, was formerly known as Czech dysplasia.

Prevalence

The exact prevalence of type II collagen disorders is not known. However, Stickler syndrome, *COL2A1*-related, may be the most common type II collagen disorder; the overall incidence of all types of Stickler syndrome is estimated at 1:10,000 [Rose et al 2001].

2. Evaluation Strategies to Identify the Genetic Cause of a Type II Collagen Disorder in a Proband

Establishing a specific genetic cause of a type II collagen disorder:

- Can aid in discussions of prognosis (which are beyond the scope of this *GeneReview*) and genetic counseling;
- Is based on clinical and radiologic findings and the identification of a pathogenic variant in *COL2A1*, and involves medical history, physical examination, radiographs, family history, and molecular genetic testing.
- Note: As no formal clinical diagnostic criteria exist, specific diagnosis should be confirmed by genetic testing.

Medical history. A type II collagen disorder should be suspected in a fetus or individual with classic disease hallmarks of short stature, skeletal dysplasia, ocular manifestations (early cataract, myopia, vitreous abnormalities, retinal detachment), small jaw, cleft palate (Pierre Robin sequence), flat midface, hearing impairment, joint hypermobility, and early-onset arthrosis (see Table 1).

Physical examination. A physical examination should include standard growth parameters (height, weight, head circumference) and address the following key issues: body proportions, craniofacial features (flat facial

profile, hypertelorism, cleft palate, and retrognathia), spine, and joints (joint enlargement, hypermobility, contractures).

Imaging. Specific radiographic findings are associated with each type II collagen disorder (see Table 1).

Family history. A three-generation family history should be taken, with attention to relatives with clinical and radiographic manifestations of type II collagen disorders (e.g., specific questions about cleft palate, joint pain/deterioration, sudden visual loss / retinal detachment, hearing loss). Relevant findings from direct examination or review of medical records (including results of molecular genetic testing) must be documented.

Molecular genetic testing approaches can include **single-gene testing** and use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *COL2A1* detects missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications. Single-gene testing of *COL2A1* can be considered if clinical findings and/or family history indicate that pathogenic variants in *COL2A1* are most likely (see Table 1).
- **A multigene panel** that includes *COL2A1* and other genes of interest (see Table 2a and Table 2b) should be considered, particularly in instances with diagnostic uncertainty (e.g., prenatal evaluations), to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended.

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

3. Differential Diagnosis of Type II Collagen Disorders

The differential diagnosis of type II collagen disorders includes a range of disorders, from severe often lethal skeletal dysplasia with abnormal ossification and major skeletal abnormalities to milder conditions with limited clinical and radiographic findings. Disorders with a known genetic etiology are listed in Table 2a; disorders of unknown or multifactorial etiology are listed in Table 2b.

Table 2a. Disorders with Known Genetic Etiology to Consider in the Differential Diagnosis of Type II Collagen Disorders

Gene(s)	Disorder	MOI	Clinical Features of Disorder	
			Overlapping w/type II collagen disorders	Distinguishing from type II collagen disorders
Most severe [1]				
ALPL	Hypophosphatasia	AD AR	Poor/delayed ossification	Absence of ossification of skull & posterior elements of vertebrae; low serum ALP; no type II collagen extraskeletal characteristic abnormalities [2]

Table 2a. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Features of Disorder	
			Overlapping w/type II collagen disorders	Distinguishing from type II collagen disorders
COL1A1 *COL1A2* *CRTAP* *P3H1* (*LEPRE1*) *PPIB*	Severe osteogenesis imperfecta (See *COL1A1*/2 Osteogenesis Imperfecta.)	AD AR	Poor/delayed ossification; short limbs	Multiple fractures & deformities of long bones; no type II collagen extraskeletal characteristic abnormalities [2]
HSPG2	Dyssegmental dysplasia (OMIM 224410) (incl Silverman-Handmaker & Rolland-Desbuquois types)	AR	Narrow chest; short limbs; cleft palate	Vertebral disorganization; marked differences in size & shape of vertebral bodies (anisospondyly); bowed long bones
SLC26A2	Achondrogenesis type 1B	AR	Poor ossification; flat face; short neck; hydropic appearance	Crescent-shaped ilia; extremely short limbs w/loss of longitudinal orientation; short fingers & toes; hypoplasia of thorax; protuberant abdomen
SLC26A2	*SLC26A2*-related atelosteogenesis	AR	Often delayed ossification of upper thoracic vertebra & pubic bone; short limbs; cleft palate; distinctive facial features (midface retrusion, depressed nasal bridge, micrognathia)	Hitchhiker (abducted) thumbs; poor/delayed ossification less severe than in severe type II collagen disorders; distal tapering of humeri; hypoplastic fibulae
SLC26A2	Diastrophic dysplasia	AR	Short limbs; spine & joint deformities	Hitchhiker thumbs/toes
TRIP11	Achondrogenesis, *TRIP11*-related (OMIM 200600)	AR	Poor/delayed ossification; hydropic appearance	Poorly ossified skull bones; short, thin, easily fractured ribs; tubular bones more severely shortened & bowed
Severe to moderately severe [3]				
TRPV4	Metatropic dysplasia (See Autosomal Dominant *TRPV4* Disorders.)	AD	Limb shortening; spine & joint deformities	Narrow transverse diameter of thorax; vertebral bodies diamond/oval shape; no coronal clefts; medially placed (inset) pedicles; more distal flaring in femur & proximal tibia; most often no facial, ophthalmic, or auditory abnormalities; [2] normal ossification of skeleton
Intermediate severity [4]				
CCN6	Progressive pseudorheumatoid dysplasia (SED w/progressive arthropathy)	AR	Joint pain, multiple joint contractures, & prominent interphalangeal joints; short stature; moderate platyspondyly; widening of metaphyses; enlarged epiphyses; early osteoarthritis	No facial, ophthalmic, or auditory abnormalities; [2] toes distinct from SED w/metatarsal shortening [5]

Table 2a. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Features of Disorder	
			Overlapping w/type II collagen disorders	Distinguishing from type II collagen disorders
COL9A1 *COL9A2* *COL9A3* *COL11A1* *COL11A2*	Stickler syndrome types 2, 3, 4, & 5	AD AR	Craniofacial, ophthalmic, & auditory abnormalities; skeletal manifestations on radiographs (spondyloepiphyseal dysplasia) & joint involvement	Ophthalmologic complications often less severe than Stickler syndrome, *COL2A1*-related; ocular phenotypes in other Stickler types most often comprise type 2 congenital vitreous anomaly ("beaded" vitreous phenotype)
COL9A1 *COL9A2* *COL9A3* *COMP* *MATN3*	Multiple epiphyseal dysplasia, autosomal dominant	AD	Presents in early childhood, usually w/pain in hips &/or knees	No facial, ophthalmic, or auditory abnormalities; [2] often no spine involvement
SLC26A2	*SLC26A2*-related multiple epiphyseal dysplasia	AR	Presents in early childhood, usually w/pain in hips &/or knees; brachydactyly	No facial, ophthalmic, or auditory abnormalities; [2] clubfeet; cleft palate; double-layered patella observed on lateral knee radiographs in 60%; often no spine involvement

AD = autosomal dominant; ALP = alkaline phosphatase; AR = autosomal recessive; MOI = mode of inheritance; SED = spondyloepiphyseal dysplasia

1. The most severe type II collagen disorders include *COL2A1*-related achondrogenesis, hypochondrogenesis, and platyspondylic dysplasia, type Torrance. These disorders can be very difficult to distinguish prenatally.

2. Comprising characteristic type II collagen ocular, auditory, and orofacial abnormalities (i.e., high myopia, retinal detachment, hearing impairment, Pierre Robin sequence)

3. Severe to moderately severe type II collagen disorders include *COL2A1*-related Kniest dysplasia, spondyloepiphyseal dysplasia congenita (SEDC), and spondyloepimetaphyseal dysplasia (SEMD).

4. Intermediate severity type II collagen disorders include *COL2A1*-related spondyloperipheral dysplasia, spondyloepiphyseal dysplasia (SED) with metatarsal shortening, and Stickler syndrome.

5. Shortening of the third and/or fourth toes is a classic distinguishing hallmark of SED with metatarsal shortening.

Table 2b. Disorders of Unknown Etiology to Consider in the Differential Diagnosis of Type II Collagen Disorders

Disorder	Clinical Features of Disorder	
	Overlapping w/type II collagen disorders	Distinguishing from type II collagen disorders
Intermediate severity [1]		
Juvenile idiopathic arthritis	Presents in childhood, usually w/joint pain	No facial, ophthalmic, or auditory abnormalities [2]
Calve-Legg-Perthes [3]	Presents in childhood, usually w/hip pain	No facial, ophthalmic, or auditory abnormalities; [2] often unilateral, & if bilateral (10%-15% of affected individuals), often asynchronous involvement (femoral heads in different stages of disease); no spine involvement
Mild severity [4]		
Rheumatoid arthritis	Joint pain; radiographic skeletal changes of osteoarthritis	More pronounced clinical & laboratory signs of inflammation

Table 2b. continued from previous page.

Disorder	Clinical Features of Disorder	
	Overlapping w/type II collagen disorders	Distinguishing from type II collagen disorders
Juvenile idiopathic arthritis	Joint pain	No facial, ophthalmic, or auditory abnormalities; [2] often presents at younger age

1. Intermediate severity type II collagen disorders include *COL2A1*-related spondyloperipheral dysplasia, spondyloepiphyseal dysplasia (SED) with metatarsal shortening, and Stickler syndrome. Note: Shortening of the third and/or fourth toes is a classic distinguishing hallmark of SED with metatarsal shortening.
2. Comprising characteristic type II collagen ocular, auditory, and orofacial abnormalities (i.e., high myopia, retinal detachment, hearing impairment, Pierre Robin sequence)
3. COL2A1 pathogenic variants have been associated with a Calve-Legg-Perthes-like phenotype (more accurately dysplastic proximal femoral epiphyses). Bilateral hip involvement, especially symmetrical and synchronous, is suggestive of a type II collagen disorder. Bilateral involvement of femoral heads (including different stages of severity) warrants further attention and workup in general.
4. Mild severity type II collagen disorders include *COL2A1*-related mild SED w/premature arthrosis.

4. Management

Clinical practice guidelines for type II collagen disorders have been published [Savarirayan et al 2019].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with a type II collagen disorder, the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Type II Collagen Disorders: Recommended Evaluations Following Initial Diagnosis

System/ Concern	Evaluation	Comment
Skeleton	Complete radiographic survey if indicated	• Often already performed to establish diagnosis • To assess extent of skeletal malformations
Cervical spine	• Flexion-extension radiograph • Flexion-extension MRI if instability & compression seen on radiographs or interpretation on radiographs is limited (e.g., in young persons w/ delayed ossification in upper cervical spine)	Evaluate for cervical instability & risk of spinal cord compression.
Thoracolumbar spine	Clinical exam & radiographs where indicated	Evaluate for progressive scoliosis.
Respiratory	• Pulmonary function tests • Polysomnography	• To assess extent of respiratory insufficiency in severe presentations (PRS, small thorax, pulmonary hypoplasia) • To identify sleep apnea (central sleep apnea as result of unrecognized unstable cervical spine, obstructive sleep apnea as result of tracheobronchomalacia & cleft palate sequelae) • To identify respiratory insufficiency in those w/severe kyphoscoliosis
Eyes	Dilated eye exam	Preferably by expert ophthalmologist familiar w/ophthalmic complications (e.g., high myopia, vitreous changes, retinal detachment, early cataract, vision problems, blindness) in type II collagen disorders

Table 3. continued from previous page.

System/ Concern	Evaluation	Comment
ENT/Mouth	• Hearing eval • Eval for cleft palate	
Feeding	Swallowing assessment	In persons w/PRS
Musculoskeletal	• Clinical exam • Referral to orthopedic surgeon if indicated • Referral to PT if indicated	Functional testing / activities of daily living should be considered
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of type II collagen disorders to facilitate medical & personal decision making
Psychosocial issues	Awareness & referral to resources	Issues related to short stature, dysmorphic facial features, poor eyesight &/or hearing impairment, pain, etc.

Adapted from Savarirayan et al [2019]
MOI = mode of inheritance; PRS = Pierre Robin sequence; PT = physical therapist
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 4).

Table 4. Type II Collagen Disorders: Treatment of Manifestations

Manifestation/ Concern	Treatment	Considerations/Other
Cervical spine instability w/ spine compression	Surgical mgmt for medullopathy (C1-C2 fixation)	Mgmt by expert familiar w/rare skeletal dysplasia & spine involvement
Scoliosis	Surgery for severe, progressive scoliosis	In young children, progressive scoliosis can be treated non-surgically (e.g., brace).
Respiratory insufficiency	• Supported ventilation (e.g., CPAP) • Surgery for cleft palate	
Sleep apnea	• Referral to pulmonologist & sleep medicine physician • Supported ventilation (e.g., CPAP) • Surgery for PRS	In case of central sleep apnea as result of unrecognized unstable cervical spine, referral for eval & mgmt
Cleft palate	Surgical repair	
High myopia, vitroretinal complications, & early cataract	• Refractive errors should be corrected w/ spectacles. • Persons at risk should be informed about signs & symptoms of retinal detachment & advised about immediate eval & treatment when symptoms occur.	• Mgmt of vitreoretinal complications by expert ophthalmologist familiar w/ ophthalmic complications • Consider prophylactic retinopexy in Stickler syndrome, *COL2A1*-related.
Hearing impairment	Hearing aids &/or surgery if indicated	
Joint problems (laxity, contractures, pain due to early-onset arthrosis)	• Referral to orthopedic surgeon for eval • Referral to PT • Referral to OT if indicated • Analgesics	• Advice on joint-friendly activities (e.g., swimming, cycling) • Consider need for mobility device. • Avoidance of physical activities that strain joints when possible

Table 4. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Lower-limb malalignment	• Guided growth surgery • Osteotomy	
Obesity	Referral to clinical nutritionist	Even if weight is normal, importance of avoiding obesity should be emphasized.
Psychosocial problems	• Referral to resources • Referral to psychologist	

Adapted from Savarirayan et al [2019]
CPAP = continuous positive airway pressure; OT = occupational therapist; PRS = Pierre Robin sequence; PT = physical therapist

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 5 are recommended.

Table 5. Type II Collagen Disorders: Recommended Surveillance

System/ Concern	Evaluation	Frequency
General health	Physical exam	Annually or as indicated
Cervical spine	• Flexion-extension radiograph • Flexion-extension MRI if instability & compression on radiographs or limited interpretation on radiographs	Every 2-3 yrs in those w/severe type II collagen disorder & no instability
Thoracolumbar spine	• Clinical exam • Radiographs when indicated	Every 6-12 mos depending on severity
Respiratory	• Pulmonary function tests • Polysomnography	On regular basis in persons w/severe type II collagen disorder or severe progressive kyphoscoliosis
Eyes	Dilated eye exam	• Annually unless complications • Consider prophylactic retinopexy in Stickler syndrome, *COL2A1*-related.
ENT/Mouth	• Hearing eval • Eval for cleft palate & palatal insufficiency	Every 6-12 mos depending on severity
Feeding	Swallowing assessment	On regular basis until normal feeding
Musculoskeletal	• Clinical exam • Referral to orthopedic surgeon if indicated • Referral to PT if indicated	Annually or as indicated
Obesity	Weight	
Psychosocial concerns	Specific attention to any issues when taking history & during physical exam	

Adapted from Savarirayan et al [2019]
PT = physical therapist

Agents/Circumstances to Avoid

In individuals with cervical spine instability, extreme neck extension and neck flexion and contact sports should be avoided.

In case of general anesthesia, the cervical spine should be assessed by imaging prior to the procedure [White et al 2017].

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual in order to identify as early as possible those who would benefit from recommended surveillance in order to avoid/prevent common complications.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

In individuals with a small pelvis, delivery by cesarean section should be considered. However, each individual should be assessed by an obstetrician familiar with skeletal dysplasia [Savarirayan et al 2018].

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

5. Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Type II collagen disorders are typically inherited in an autosomal dominant manner.

Autosomal recessive inheritance of type II collagen disorders has been reported in several families to date [Tham et al 2015, Barat-Houari et al 2016a, Al-Sannaa et al 2020, Girisha et al 2020, Zhang et al 2021, Tüysüz et al 2023].

Autosomal Dominant Inheritance – Risk to Family Members

Parents of a proband

- Most individuals diagnosed with a severe type II collagen disorder have the disorder as the result of a *de novo* pathogenic variant. The overall proportion of individuals with a type II collagen disorder caused by a *de novo COL2A1* pathogenic variant is unknown.
- Many individuals diagnosed with a milder type II collagen disorder have an affected parent. Clinical variability within a family can be extensive; however, severe and mild forms are not seen in family members with the same pathogenic variant (i.e., the specific type II collagen diagnosis appears to run true in a family, but with variable expressivity).
- If the proband appears to be the only affected family member (i.e., a simplex case), molecular genetic testing is recommended for the parents of the proband to evaluate their genetic status and inform recurrence risk assessment. Note: A proband may appear to be the only affected family member because of

failure to recognize the disorder in mildly affected family members. Therefore, *de novo* occurrence of a *COL2A1* pathogenic variant in the proband cannot be confirmed unless molecular genetic testing has demonstrated that neither parent has the *COL2A1* pathogenic variant.

- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with gonadal (or somatic and gonadal) mosaicism * [Nagendran et al 2012, Okamoto et al 2012, Stevenson et al 2012, Yamamoto et al 2020, Morrison et al 2020]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.

    * A parent with somatic and gonadal mosaicism for a *COL2A1* pathogenic variant may be mildly/minimally affected.

Sibs of a proband. The risk to the sibs of the proband depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the *COL2A1* pathogenic variant identified in the proband, the risk to the sibs of inheriting the pathogenic variant is 50%.
- Penetrance in type II collagen disorders is high; however, intrafamilial variability among heterozygous family members can be extensive. Note: Severe and mild forms are not seen in family members with the same pathogenic variant (i.e., the specific type II collagen diagnosis appears to run true in a family, but with variable expressivity).
- If the *COL2A1* pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is slightly greater than that of the general population because of the possibility of parental gonadal mosaicism [Nagendran et al 2012, Okamoto et al 2012, Stevenson et al 2012, Morrison et al 2020, Yamamoto et al 2020].
- If the parents have not been tested for the *COL2A1* pathogenic variant but are clinically unaffected, the risk to the sibs of a proband appears to be low. However, sibs of a proband with clinically unaffected parents are still presumed to be at increased risk for a type II collagen disorder because of the possibility of reduced penetrance in a heterozygous parent and the possibility of parental gonadal mosaicism.

Offspring of a proband

- Each child of an individual with a type II collagen disorder has a 50% chance of inheriting the *COL2A1* pathogenic variant.
- Because many individuals with short stature have reproductive partners with short stature, offspring of individuals with a type II collagen disorder may be at risk of having double heterozygosity for two dominantly inherited bone growth disorders. The phenotypes of these individuals are distinct from those of the parents, and the affected individuals may have serious sequelae and poor outcomes [Unger et al 2001, Flynn & Pauli 2003].

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the pathogenic variant, the parent's family members may be at risk.

Autosomal Recessive Inheritance – Risk to Family Members

Parents of a proband

- The parents of an affected individual are presumed to be heterozygous for a *COL2A1* pathogenic variant.

- Molecular genetic testing is recommended for the parents of a proband to confirm that both parents are heterozygous for a *COL2A1* pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- In the families described by Tham et al [2015] and Barat-Houari et al [2016a], one heterozygous father presented with high myopia, asymmetric lower limbs, and average stature; one heterozygous mother was 154 cm tall; and the two other heterozygous parents were of normal stature.

Sibs of a proband

- If both parents are known to be heterozygous for a *COL2A1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being heterozygous, and a 25% chance of inheriting neither of the familial pathogenic variants.
- Heterozygous sibs are predicted to be either unaffected or mildly affected. Homozygous sibs will be affected in a manner similar to the affected individual but, because of variable expressivity, may have a more or less severe clinical outcome.

Offspring of a proband. Unless an affected individual's reproductive partner also has *COL2A1* pathogenic variant(s), the proband's offspring will be obligate heterozygotes for a pathogenic variant in *COL2A1*.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected.

Prenatal Testing and Preimplantation Genetic Testing

Once the *COL2A1* pathogenic variant(s) have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal and preimplantation genetic testing. While most health care professionals would consider use of prenatal and preimplantation genetic testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **MedlinePlus**
  COL2A1 gene
- **MedlinePlus**
  Stickler syndrome
- **Stickler Involved People**
  sticklers.org
- **Stickler Syndrome UK**
  United Kingdom
  Phone: 0800 066 8273
  Email: contact@stickler.org.uk
  stickler.org.uk
- **Little People of America**
  Phone: 888-LPA-2001; 714-368-3689
  Fax: 707-721-1896
  Email: info@lpaonline.org
  lpaonline.org
- **Little People UK**
  United Kingdom
  Phone: 07925893398
  Email: admin@littlepeopleuk.org
  littlepeopleuk.org
- **Short Statured People of Australia**
  Australia
  Email: info@sspa.org.au
  sspa.org.au
- **Skeletal Dysplasia Management Consortium**
  skeletaldysplasia.org
- **UCLA International Skeletal Dysplasia Registry (ISDR)**
  Phone: 310-825-8998
  International Skeletal Dysplasia Registry

Chapter Notes

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