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Type II Collagen Disorders Overview

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Summary

The purpose of this overview is to increase the awareness of clinicians regarding type II collagen disorders and their management.

The following are the goals of this overview.

Goal 1

Describe the clinical characteristics of type II collagen disorders.

Goal 2

Provide an evaluation strategy to identify the genetic cause of a type II collagen disorder in a proband.

Goal 3

Inform genetic counseling of family members of an individual with a type II collagen disorder.

Goal 4

Review management of type II collagen disorders.

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

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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. Included in this overview are the following specific type II collagen phenotypes (disorders included in the Nosology and Classification of Genetic Skeletal Disorders: 2015 Revision) [Bonafe et al 2015], which can be grouped according to severity.

Most severe (often lethal perinatally)

- Achondrogenesis type II
- Hypochondrogenesis
- Platyspondylic dysplasia, Torrance type

Severe/moderately severe (neonatal presentation)

- Kniest dysplasia
- Spondyloepiphyseal dysplasia congenita (SEDC)
- Spondyloepimetaphyseal dysplasia (SEMD), Strudwick type

Intermediate (neonatal/childhood/adolescent presentation)

- Spondyloperipheral dysplasia
- Spondyloepiphyseal dysplasia with metatarsal shortening
- Stickler syndrome type 1

Mild (adolescent/adult presentation). Mild spondyloepiphyseal dysplasia (SED) with premature arthrosis

Phenotypes

Considerable phenotypic overlap notwithstanding, discriminating features can aid in the specific diagnosis (see Table 1). The following individual phenotypes are recognized.

Achondrogenesis type II is the most severe type II collagen disorder. Achondrogenesis type II 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 due to cardiorespiratory failure [Spranger et al 2012b].

Hypochondrogenesis 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 type II. 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].

Platyspondylic dysplasia, Torrance type 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].

Kniest dysplasia 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 dyplasia 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 due to hypoplasia of 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].

Spondyloepiphyseal dysplasia congenita (SEDC). Individuals with SEDC present neonatally with severe disproportionate short stature, short extremities (<5th percentile), 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), and individuals with SEDC are also at greater risk for tracheolaryngomalacia and related respiratory complications.

SEDC cannot be distinguished from SEMD, Strudwick type 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), Strudwick type. Infants with SEMD, Strudwick type initially present with the same clinical and radiographic findings as those with SEDC. However, within the first year of life, metaphyseal flaring becomes evident, suggesting this diagnosis. The clinical course is similar to that of SEDC, 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].

Spondyloperipheral dysplasia 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].

Spondyloepiphyseal dysplasia (SED) with metatarsal shortening (formerly Czech dysplasia) 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 endplates, 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].

Stickler syndrome type 1 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 endplate 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].

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].

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

Type II Collagen Disorder: Most severe – often perinatal lethal [1]	Age of Diagnosis	Poor/ Delayed Ossification	Stature	Extraskeletal Abnormalities	Distinguishing Feature(s) [2]	
					Clinical	Radiographic
Achondrogenesis type II	Prenatal	++++++	Extremely short	• Flat midface • PRS • Hydropic appearance	Often delivered prematurely, stillborn or die shortly after birth (hrs)	• Absent or severely retarded 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
Hypochondro-genesis	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 the prenatal period • Short ribs • Vertebral bodies are small & ovoid,

Table 1. continued from previous page.

Type II Collagen Disorder: Most severe – often perinatal lethal [1]	Age of Diagnosis	Poor/ Delayed Ossification	Stature	Extraskeletal Abnormalities	Distinguishing Feature(s) [2]	
					Clinical	Radiographic
						& unossified in cervical region. • Pubic bones are unossified. • Hypoplastic ilia • Short & relatively broad long bones w/ delayed ossification in distal femoral & proximal tibial epiphysis
Platyspondylic dysplasia, Torrance type	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	**Age of diagnosis**	**Poor/ delayed ossification**	**Stature**	**Extraskeletal abnormalities**	**Distinguishing feature(s) [2]**	
					Clinical	**Radiographic**
Kniest dysplasia	Perinatal	++++	Short	• PRS • High prevalence of myopia, lens subluxation, retinal detachment, & other vitreal abnormalities • ↑ risk of tracheo-laryngomalacia	• 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 long bones (large metaphyses & epiphyses)

Table 1. continued from previous page.

Type II Collagen Disorder: Most severe – often perinatal lethal [1]	Age of Diagnosis	Poor/ Delayed Ossification	Stature	Extraskeletal Abnormalities	Distinguishing Feature(s) [2]	
					Clinical	Radiographic
SEDC	Perinatal	+++	Short	• Flat facial profile, hypertelorism, PRS • Ocular abnormalities • ↑ risk of tracheo-laryngomalacia	• 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 Strudwick type	Perinatal	+++	Short	• Flat facial profile, hypertelorism, PRS • Ocular abnormalities • ↑ risk of tracheo-laryngomalacia	• Severe disproportionate short stature & short extremities (˂5th percentile) • ↑ risk of cervical instability & spinal cord compression	• 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/child/ adult	**Age of diagnosis**	**Poor/ delayed ossification**	**Stature**	**Extraskeletal abnormalities**	**Distinguishing feature(s) [2]**	
					Clinical	**Radiographic**
Spondylo-peripheral 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

Table 1. continued from previous page.

Type II Collagen Disorder: Most severe – often perinatal lethal [1]	Age of Diagnosis	Poor/ Delayed Ossification	Stature	Extraskeletal Abnormalities	Distinguishing Feature(s) [2]	
					Clinical	Radiographic
SED with metatarsal shortening	Before adolescence	Normal	Average	Usually no extraskeletal abnormalities	• Typical phenotypic hallmark: shortening of 3rd & 4th toes • Severe joint pain	• Platyspondyly w/irregular endplates • Narrowed intervertebral spaces • Early osteoarthrosis in spine & lower limb joints (deformed femoral heads & dysplastic pelvis) • Metatarsal hypoplasia involving postaxial toes
Stickler type 1	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	**Age of diagnosis**	**Poor/ delayed ossification**	**Stature**	**Extraskeletal abnormalities**	**Distinguishing feature(s) [2]**	
					Clinical	**Radiographic**
Mild SED with premature-onset arthrosis	Adolescence/ adult	Normal	Average	Vision, hearing, & orofacial structures are usually normal.	Progressive joint pain & limitation of motion of the hip & knee joint	Epiphyseal dysplasia & early-onset osteoarthrosis

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

1. Can be very difficult to distinguish antenatally

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

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, 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 collagen type II disorders (e.g., achondrogenesis type II; hypochondrogenesis; platyspondyly, Torrance type; SEDC; and SEMD, Strudwick type).
- In Kniest dysplasia 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 [Hoornaert et al 2007].
- In Stickler syndrome type 1, 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 cases 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 the 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 type II was formerly known as Langer-Saldino dysplasia.

Spondyloperipheral dysplasia is also referred to as spondyloperipheral dysplasia-short ulna syndrome.

Spondyloepiphyseal dysplasia with metatarsal shortening is also referred to as Czech dysplasia.

Prevalence

The exact prevalence of type II collagen disorders is not known. However, Stickler syndrome type 1 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].

Differential Diagnosis

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 (from most to least severe) 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

Type II Collagen Disorder	Differential Diagnosis Disorder	Gene(s)	MOI	Clinical Features of Differential Diagnosis Disorder	
				Overlapping w/type II collagen disorders	Distinguishing from type II collagen disorders
Most severe [1] – achondrogenesis type II; hypochondrogenesis;	Severe OI (see COL1A1/2-OI)	*COL1A1* *COL1A2* *CRTAP* *P3H1*	AD AR	• Poor/delayed ossification • Short limbs	• Multiple fractures & deformities of long bones

Table 2a. continued from previous page.

Type II Collagen Disorder	Differential Diagnosis Disorder	Gene(s)	MOI	Clinical Features of Differential Diagnosis Disorder	
				Overlapping w/type II collagen disorders	Distinguishing from type II collagen disorders
platyspondylic dysplasia, Torrance type		(*LEPRE1*) *PPIB*			• No extraskeletal type II collagen characteristic abnormalities [2]
	Hypophosphatasia	*ALPL*	AD AR	Poor/delayed ossification	• Absent ossification of the skull • Absent ossification of posterior elements of vertebrae • Low serum ALP • No extraskeletal type II collagen characteristic abnormalities [2]
	Achondrogenesis type 1A (OMIM 200600)	*TRIP11*	AR	• Poor/delayed ossification • Hydropic appearance	• Poorly ossified skull bones • Short, thin, easily fractured ribs • Tubular bones more severely shortened & bowed
	Achondrogenesis type 1B	*SLC26A2*	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
	Atelosteogenesis type 2	*SLC26A2*	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 severe type II collagen disorder • Distal tapering of humeri • Hypoplastic fibulae
	Diastrophic dysplasia	*SLC26A2*	AR	• Short limbs • Spine & joint deformities	Hitchhiker thumbs/toes
	Dyssegmental dysplasia, Silverman-Handmaker type (OMIM 224410) (may include Rolland-Desbuquois type)	*HSPG2*	AR	• Narrow chest • Short limbs • Cleft palate	• Vertebral disorganization • Marked differences in size & shape of vertebral bodies (anisospondyly) • Bowed long bones

Table 2a. continued from previous page.

Type II Collagen Disorder	Differential Diagnosis Disorder	Gene(s)	MOI	Clinical Features of Differential Diagnosis Disorder	
				Overlapping w/type II collagen disorders	Distinguishing from type II collagen disorders
Severe to moderately severe – Kniest dysplasia; SEDC; SEMD, Strudwick type	Metatropic dysplasia (see TRPV4-Associated Disorders	*TRPV4*	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 – spondyloperipheral dysplasia; SED w/ metatarsal shortening (Czech dysplasia); [3] Stickler syndrome type 1	MED, AD	*COL9A1* *COL9A2* *COL9A3* *COMP* *MATN3*	AD	Presents in early childhood, usually w/pain in hips &/or knees	• No facial, ophthalmic, or auditory abnormalities [2] • Often no spine involvement
	MED, recessive	*SLC26A2*	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
	Progressive pseudorheumatoid dysplasia (SED w/progressive arthropathy)	*CCN6*	AR	• Joint pain, multiple joint contractures, & prominent interphalangeal joints • Short stature • Moderate platysplondyly • Widening of the metaphyses, enlarged ephiphyses • Early osteoarthritis	• No facial, ophthalmic, or auditory abnormalities [2] • Toes are distinct from SED w/metatarsal shortening [3]

Table 2a. continued from previous page.

Type II Collagen Disorder	Differential Diagnosis Disorder	Gene(s)	MOI	Clinical Features of Differential Diagnosis Disorder	
				Overlapping w/type II collagen disorders	Distinguishing from type II collagen disorders
	Stickler syndrome types 2, 3, 4, & 5	*COL11A1* *COL11A2* *COL9A1* *COL9A2* *COL9A3*	AD AR	• Craniofacial, ophthalmic, & auditory abnormalities • Skeletal manifestations on x-ray (spondyloepiphyseal dysplasia) & joint involvement	• Ophthalmologic complications often less severe than Stickler type 1 • Ocular phenotypes in other Stickler subtypes most often comprise type 2 congenital vitreous anomaly ("beaded" vitreous phenotype).

AD = autosomal dominant; ALP = alkaline phosphatase test; AR = autosomal recessive; OI = osteogenesis imperfecta; MED = multiple epiphyseal dysplasia; MOI = mode of inheritance; SED = spondyloepiphyseal dysplasia; SEDC = spondyloepiphyseal dysplasia congenita; SEMD = spondyloepimetaphyseal dysplasia
1. Can be very difficult to distinguish antenatally
2. Comprising characteristic type II collagen ocular, auditory, and orofacial abnormalities (i.e., high myopia, retinal detachment, hearing impairment, Pierre Robin sequence)
3. Shortening of the third and/or fourth toes is a classic distinguishing hallmark of SED with metatarsal shortening (Czech dysplasia).

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

Type II Collagen Disorder	Differential Diagnosis Disorder	Clinical Features of Differential Diagnosis Disorder	
		Overlapping w/type II collagen disorders	Distinguishing from type II collagen disorders
Intermediate severity – spondyloperipheral dysplasia; SED w/metatarsal shortening (Czech dysplasia) [1]; Stickler syndrome type 1	Juvenile idiopathic arthritis	Presents in childhood, usually w/ joint pain	No facial, ophthalmic, or auditory abnormalities [3]
	Calve-Legg Perthes [2]	Presents in childhood, usually w/hip pain	• No facial, ophthalmic, or auditory abnormalities [3] • Often unilateral, & if bilateral (10%-15% of cases) often asynchronous involvement (femoral heads in different stages of disease) [2] • No spine involvement
Mild severity – mild SED w/premature arthrosis	Rheumatoid arthritis	• Joint pain • Radiographic skeletal changes of osteoarthritis	More pronounced clinical & laboratory signs of inflammation
	Juvenile idiopathic arthritis	Joint pain	• No facial, ophthalmic, or auditory abnormalities [3] • Often presents at younger age

AD = autosomal dominant; ALP = alkaline phosphatase test; AR = autosomal recessive; MED = multiple epiphyseal dysplasia; MOI = mode of inheritance; OI = osteogenesis imperfecta; SED = spondyloepiphyseal dysplasia; SEDC = spondyloepiphyseal dysplasia congenita; SEMD = spondyloepimetaphyseal dysplasia
1. Shortening of the third and/or fourth toes is a classic distinguishing hallmark of spondyloepiphyseal dysplasia (SED) with metatarsal shortening (Czech dysplasia).
2. 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) warrant further attention and workup in general.
3. Comprising characteristic type II collagen ocular, auditory, and orofacial abnormalities (i.e., high myopia, retinal detachment, hearing impairment, PRS)

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

A collagen type II disorder should be suspected in fetuses and individuals presenting with classic or suggestive clinical and radiologic findings of collagen type II dysfunction.

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, x-rays, family history, and genetic testing.

  Note: As no formal clinical diagnostic criteria exist, specific diagnosis should be confirmed by genetic testing.

Medical history. A collagen type II disorder should be suspected in a fetus or individuals 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, widely spaced eyes, retrognathia, and cleft palate), spine, and joints (joint enlargement, hypermobility, contractures). 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 small intragenic deletions/insertions and missense, nonsense, and splice site variants; 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 this particular gene 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 at the most reasonable time and cost 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. Genetic Counseling

Mode of Inheritance

Type II collagen disorders are inherited in an autosomal dominant manner. However, rare cases of autosomal recessive inheritance in spondyloepiphyseal dysplasia congenita have been reported [Tham et al 2015, Barat-Houari et al 2016a].

Risk to Family Members

Autosomal Dominant Inheritance

Parents of a proband

- Most individuals diagnosed with a severe form of type II collagen disorder have the disorder as the result of a *de novo* pathogenic variant. The overall proportion of cases caused by a *COL2A1de novo* pathogenic variant is unknown.
- Many individuals diagnosed with the milder form of 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).
- Recommendations for the parents of a proband with an apparent *de novo* pathogenic variant include molecular genetic testing and clinical examination (see Evaluation of Relatives at Risk).
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband and somatic and/or germline mosaicism in a parent. The incidence of somatic and germline mosaicism is unknown, but it is likely rare since only a few cases of genetically proven somatic and germline mosaicism have been reported in the literature [Nagendran et al 2012, Okamoto et al 2012, Stevenson et al 2012].
- The family history of some individuals diagnosed with a milder form of type II collagen disorder may appear to be negative because of failure to recognize the disorder in mildly affected family members. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of the proband.
- Note: If the parent is the individual in whom the *COL2A1* pathogenic variant first occurred, s/he may have somatic mosaicism for the variant and 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 is 50%. 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 *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 germline mosaicism, with or without somatic mosaicism [Nagendran et al 2012, Okamoto et al 2012, Stevenson et al 2012].
- 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 parental somatic and/or germline mosaicism or reduced penetrance in a heterozygous parent.

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.

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, his or her family members may be at risk.

Autosomal Recessive Inheritance

Parents of a proband

- The parents of an affected individual are obligate heterozygotes for one *COL2A1* pathogenic variant.
- To date, autosomal recessive spondyloepiphyseal dysplasia congenita has been reported in two families [Tham et al 2015, Barat-Houari et al 2016a]. In these families: one heterozygous father presented with high myopia, asymmetric lower limbs, and average stature; one heterozygous mother was 154 cm tall; the two other heterozygous parents were of normal stature.

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of inheriting two *COL2A1* pathogenic variants (one from each heterozygous parent), a 50% chance of inheriting one *COL2A1* pathogenic variant, and a 25% chance of inheriting a *COL2A1* pathogenic variant from neither parent.
- 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 individual with biallelic *COL2A1* pathogenic variants has children with an individual who also has a type II collagen disorder, his/her 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.

Considerations in families with an apparent *de novo* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the proband may have a *de novo* pathogenic variant or a parent may have somatic and/or germline mosaicism for the pathogenic variant. However, non-medical explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal 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.

DNA banking is the storage of DNA (typically extracted from white blood cells) for possible future use. Because it is likely that testing methodology and our understanding of genes, allelic variants, and diseases will improve in the future, consideration should be given to banking DNA of affected individuals.

Prenatal Testing and Preimplantation Genetic Diagnosis

Once the *COL2A1* pathogenic variant(s) have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic diagnosis are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. While most centers would consider decisions regarding prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

4. Management

Evaluations Following Initial Diagnosis

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

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Type II Collagen Disorders

System/Concern	Evaluation	Comment
Skeleton	Complete radiographic survey if indicated	• Often already performed in order to establish diagnosis • To asses 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 individuals w/ delayed ossification in upper cervical spine)	Evaluate for cervical instability & risk of spinal cord compression.
Thoracolumbar spine	Clinical examination & 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 due to unrecognized unstable cervical spine, obstructive sleep apnea due to tracheobronchomalacia & cleft palate sequelae) • To identify respiratory insufficiency in those w/severe kyphoscoliosis
Eyes	Dilated eye examination	Preferably by an expert ophthalmologist familiar w/the ophthalmic complications (e.g., high myopia, vitreous changes, retinal detachment, early cataract, vision problems, blindness)
ENT/Mouth	• Hearing evaluation • Evaluation for cleft palate	
Feeding	Swallowing assessment	In individuals w/PRS
Musculoskeletal	• Clinical examination • Referral to orthopedic surgeon if indicated • Referral to physiotherapist if indicated	Functional testing / activities of daily living should be considered.

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Genetics	Consultation w/clinical geneticist &/or genetic counselor	
Psychosocial issues	• Awareness • Referral to resources	Issues related to (e.g.) short stature, dysmorphic facial features, poor eyesight &/or hearing impairment, pain

Adapted from Savarirayan et al [2019]
PRS = Pierre Robin sequence

Treatment of Manifestations

Table 4. Treatment of Manifestations in Individuals with Type II Collagen Disorders

Manifestation/ Concern	Treatment	Considerations/Other
Cervical spine instability w/spine compression	Surgical management for medullopathy (C1-C2 fixation)	Management by an 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, CPAP • Surgery of cleft palate	
Sleep apnea	• Referral to pulmonologist & sleep medicine physician • Supported ventilation, CPAP, surgery of PRS	In case of central sleep apnea due to unrecognized unstable cervical spine, referral for evaluation & management
Cleft palate	Surgery	
High myopia, vitroretinal complications, & early cataract	• Refractive errors should be corrected w/ spectacles. • Individuals at risk should be informed about signs & symptoms of retinal detachment, & should be advised about immediate evaluation & treatment, when symptoms occur.	• Management of vitreoretinal complications by an expert ophthalmologist familiar w/the ophthalmic complications. • Consider prophylactic retinopexy in Stickler syndrome type 1 (*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 evaluation • Referral to physiotherapist • Referral to occupational therapist if indicated • Analgesics	• Advice on joint-friendly activities (e.g., swimming, cycling) • Consider need for a mobility device. • Avoidance of physical activities that strain joints, when possible
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

Surveillance

Table 5. Recommended Surveillance for Individuals with Type II Collagen Disorders

System/ Concern	Evaluation	Frequency
General health	Physical examination	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 examination • Radiographs when indicated	Every 6-12 mos, depending on severity
Respiratory	• Pulmonary function tests • Polysomnography	On a regular basis in individuals w/severe type II collagen disorder or severe, progressive kyphoscoliosis
Eyes	Dilated eye examination	• Annually unless complications • Consider prophylactic retinopexy in Stickler syndrome type 1 (*COL2A1*-related)
ENT/ Mouth	• Hearing evaluation • Evaluation for cleft palate & palatal insufficiency	Every 6-12 mos depending on severity
Feeding	Swallowing assessment	On a regular basis until normal feeding
Musculoskeletal	• Clinical examination • Referral to orthopedic surgeon if indicated • Referral to physiotherapist if indicated	Annually or as indicated
Obesity	Weight	Annually or as indicated
Psychosocial concerns	Specific attention to any issues when taking history & during physical examination	Annually or as indicated

Adapted from Savarirayan et al [2019]

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 clinical/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 regular surveillance in order to avoid/prevent common complications. Evaluations can include:

- Molecular genetic testing if the pathogenic variant in the family is known;
- Clinical examination, radiographs, eye examination, and hearing evaluation if the pathogenic variant in the family is not known.

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.

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.

- **My46 Trait Profile**
  Stickler syndrome
- **National Library of Medicine Genetics Home Reference**
  COL2A1 gene
- **National Library of Medicine Genetics Home Reference**
  Stickler syndrome
- **Stickler Involved People (SIP)**
  15 Angelina
  Augusta KS 67010
  Phone: 316-259-5194
  Email: sip@sticklers.org
  www.sticklers.org
- **Stickler Syndrome Support Group (SSSG)**
  PO Box 3351
  Littlehampton West Sussex BN16 9GB
  United Kingdom
  Phone: 01903 785771
  Email: info@stickler.org.uk
  www.stickler.org.uk
- **Little People of America, Inc. (LPA)**
  250 El Camino Real
  Suite 201
  Tustin CA 92780
  Phone: 888-572-2001 (toll-free); 714-368-3689
  Fax: 714-368-3367
  Email: info@lpaonline.org
  www.lpaonline.org
- **Little People UK**
  P.O Box 1292

Peterborough PE2 2NT
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Phone: 07925893398
Email: admin@littlepeopleuk.org
www.littlepeopleuk.org

- **Short Statured People of Australia**
  Australia
  Email: sspaenquiry@gmail.com
  www.sspa.org.au

- **International Skeletal Dysplasia Registry**
  UCLA
  615 Charles E. Young Drive
  South Room 410
  Los Angeles CA 90095-7358
  Phone: 310-825-8998
  Fax: 310-206-5266
  Email: Salon@mednet.ucla.edu
  International Skeletal Dysplasia Registry

- **Skeletal Dysplasia Management Consortium**
  www.skeletaldysplasia.org

- **Skeletal Dysplasia Network, European (ESDN)**
  Institute of Genetic Medicine
  Newcastle University, International Centre for Life
  Central Parkway
  Newcastle upon Tyne NE1 3BZ
  United Kingdom
  Email: info@esdn.org
  www.esdn.org

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