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NLM Citation: Rohrbach M, Giunta C. *PLOD1*-Related Kyphoscoliotic Ehlers-Danlos Syndrome. 2000 Feb 2 [Updated 2024 Jun 13]. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

PLOD1-Related Kyphoscoliotic Ehlers-Danlos Syndrome

Synonyms: Ehlers-Danlos Syndrome Type VIA (EDS VIA), Lysyl-Hydroxylase 1 Deficiency, *PLOD1*-kEDS

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Created: February 2, 2000; Updated: June 13, 2024.

Summary

Clinical characteristics

PLOD1-related kyphoscoliotic Ehlers-Danlos syndrome (*PLOD1*-kEDS) is characterized by hypotonia, generalized joint hypermobility, early-onset kyphoscoliosis, skin fragility, and ocular abnormality. Intelligence is normal. Life span may be normal, but affected individuals are at risk of life-threatening arterial ruptures and spontaneous dissections of medium-sized arteries. Adults with severe kyphoscoliosis are at risk for complications from restrictive lung disease, recurrent pneumonia, and cardiac failure.

Diagnosis/testing

The diagnosis of *PLOD1*-kEDS is established in a proband with characteristic clinical features and biallelic pathogenic variants in *PLOD1* identified by molecular genetic testing. If only one pathogenic variant and/or variants of uncertain significance are identified, testing for a markedly increased ratio of deoxypyridinoline to pyridinoline cross-links in urine measured by high-performance liquid chromatography (a highly sensitive, specific, and inexpensive test) may be necessary for confirmation of the diagnosis.

Management

Treatment of manifestations: Physical therapy to strengthen large muscle groups; swimming; management of kyphoscoliosis by an orthopedic surgeon, including surgery as needed; bracing to support unstable joints; protective pads and helmets during active sports; dermal wounds should be closed without tension, preferably in two layers; deep stitches should be applied generously; cutaneous stitches should be left in place twice as long as usual, and additional fixation of adjacent skin with adhesive tape can help prevent stretching of the scar; treatment of cardiovascular manifestations per a cardiologist; control of blood pressure to reduce the risk of arterial rupture; treatment with beta-blockers as needed to prevent aortic dilatation; standard American Heart Association guidelines for antimicrobial prophylaxis for mitral valve prolapse; corrective lenses for myopia

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and/or astigmatism; laser treatment of the retina for those with imminent detachment; careful stitching for hernia repair.

Surveillance: Annual physical therapy assessment for weakness and motor issues and orthopedic assessment for management of kyphoscoliosis and recurrent dislocations; assessment for osteopenia as needed beginning at age ten to 12 years; assessment for respiratory complications as needed; echocardiogram at five-year intervals beginning at age five years; consider intermittent surveillance of the entire aorta with CT or MRA beginning in young adulthood and at least annually in anyone with aortic or arterial dilatation; annual ophthalmology examination; annual examination for inguinal hernia.

Agents/circumstances to avoid: Sports that stress the joints, such as gymnastics or long-distance running; high-impact sports (collision sports); heavy lifting and weight training with extreme lifting; arteriography should be discouraged and used only to identify life-threatening sources of bleeding prior to surgical intervention because of the risk of vascular injury.

Evaluation of relatives at risk: Clarify the genetic status of apparently asymptomatic older and younger sibs of a proband in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures.

Pregnancy management: Affected pregnant women may be at increased risk for miscarriage, premature rupture of membranes, and rupture of arteries. Monitoring aortic root measurement during pregnancy by echocardiogram is recommended. Delivery should be performed in a medical center with a high-risk perinatologist in attendance.

Genetic counseling

PLOD1-kEDS is inherited in an autosomal recessive manner. If both parents are known to be heterozygous for a *PLOD1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier. If both *PLOD1* pathogenic variants have been identified in an affected family member, carrier testing for at-risk relatives and prenatal/preimplantation genetic testing are possible.

Diagnosis

Suggestive Findings

PLOD1-related kyphoscoliotic Ehlers-Danlos syndrome (*PLOD1*-kEDS) **should be suspected** in individuals with minimal criteria suggestive of *PLOD1*-kEDS.

Clinical Features

Major criteria

- Congenital muscular hypotonia
- Congenital or early-onset kyphoscoliosis (progressive or nonprogressive)
- Generalized joint hypermobility with dislocations/subluxations (shoulders, hips, and knees in particular)

Minor criteria

- Skin hyperextensibility
- Skin fragility (easy bruising, friable skin, poor wound healing, widened atrophic scarring)
- Rupture/aneurysm of a medium-sized artery
- Osteopenia/osteoporosis
- Blue sclerae, scleral and ocular fragility/rupture

- Hernia (umbilical or inguinal)
- Pectus deformity
- Marfanoid habitus
- Talipes equinovarus
- Refractive errors (myopia, hypermetropia)
- Microcornea

Minimal criteria suggestive of *PLOD1*-kEDS

- Congenital muscular hypotonia AND congenital or early-onset kyphoscoliosis; PLUS
- Either of the following:
  - Generalized joint hypermobility
  - Three minor criteria

Family History

Family history is consistent with autosomal recessive inheritance (e.g., affected sibs and/or parental consanguinity). Absence of a known family history does not preclude the diagnosis.

Establishing the Diagnosis

The diagnosis of *PLOD1*-kEDS **is established** in a proband with suggestive findings and biallelic pathogenic (or likely pathogenic) variants in *PLOD1* identified by molecular genetic testing (see Table 1). If only one pathogenic variant and/or variants of uncertain significance are identified, additional confirmatory testing (e.g., measuring urinary pyridinolines) may be necessary.

Note: (1) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this *GeneReview* is understood to include likely pathogenic variants. (2) Identification of biallelic *PLOD1* variants of uncertain significance (or of one known *PLOD1* pathogenic variant and one *PLOD1* variant of uncertain significance) does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of *PLOD1*-kEDS, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**.

- **Single-gene testing.** Sequence analysis of *PLOD1* is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If only one or no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis to detect exon and whole-gene deletions or duplications.

  Note: A common intragenic duplication caused by an Alu-Alu recombination in introns 9 and 16 accounts for approximately 30% of pathogenic variants [Brady et al 2017]. First-tier analysis of *PLOD1*, typically sequencing, should include analysis for this duplication. If this analysis does not identify one or both pathogenic variants in an individual, gene-targeted deletion/duplication analysis is performed.

- **A multigene panel** that includes *PLOD1* and other genes of interest (see Differential Diagnosis) may be considered 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) Some 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 an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited generalized connective tissue disorders, **comprehensive genomic testing** does not require the clinician to determine which gene is likely involved. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in *PLOD1*-Related Kyphoscoliotic Ehlers-Danlos Syndrome

Gene [1]	Method	Proportion of Pathogenic Variants [2] Identified by Method
PLOD1	Sequence analysis [3]	67% [4, 5]
	Gene-targeted deletion/duplication analysis [6]	33% [5]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include missense, nonsense, and splice site variants and small intragenic deletions/insertions; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Brady et al [2017]
5. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]
6. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

Additional Confirmatory Testing

Biochemical testing. Deficiency of the enzyme procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1 (PLOD1; also called lysyl hydroxylase, or LH1) results in a deficiency in hydroxylysine-based pyridinoline cross-links in collagens. Detection of an increased ratio of deoxypyridinoline (Dpyr) to pyridinoline (Pyr) cross-links in urine quantitated by high-performance liquid chromatography is a highly sensitive and specific test for *PLOD1*-kEDS. The normal ratio of Dpyr:Pyr cross-links is approximately 0.2, whereas in *PLOD1*-kEDS the ratio is approximately 6.0 [Steinmann et al 1995, Rohrbach et al 2011, Abdalla et al 2015]. Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) can be used to detect faster migration of underhydroxylated collagen chains and their derivatives.

Clinical Characteristics

Clinical Description

PLOD1-related kyphoscoliotic Ehlers-Danlos syndrome (*PLOD1*-kEDS) is characterized by hypotonia, early-onset kyphoscoliosis, and generalized joint hypermobility in association with skin fragility and ocular abnormality. To date, 94 individuals have been identified with biallelic pathogenic variants in *PLOD1* [Yeowell et al 2000, Brunk et al 2004, Walker et al 2004, Giunta et al 2005b, Walker et al 2005, Yeowell et al 2005, Yiş et al 2008, Esaka et al 2009, Voermans et al 2009, Kariminejad et al 2010, Gok et al 2012, Busch et al 2014, Tosun et al 2014, Brady et al 2017, Quade et al 2017, Henneton et al 2018, Ni et al 2020, Shin et al 2020, Conti et al 2021, Zhao et al 2021, Colman et al 2022, Yan et al 2022]. The following description of the phenotypic features associated with this condition is based on these reports.

Table 2. *PLOD1*-Related Kyphoscoliotic Ehlers-Danlos Syndrome: Frequency of Select Features

Feature	% of Persons w/Feature	Comment
Hypotonia	100%	
Gross motor delay	~60%	
Scoliosis/kyphoscoliosis	95%	
Recurrent dislocations	~30%	
Clubfoot	~20%	
Osteopenia/osteoporosis	~20%	
Skin manifestations	97%	Hyperelastic & easily stretched skin
Cardiovascular manifestations	~30%	Vascular rupture
Ocular manifestations	45%	Bluish sclerae, refractive errors, scleral & ocular fragility/rupture, microcornea
Hernias	~15%	Umbilical or inguinal

Prenatal. Pregnancy involving an affected fetus may be complicated by premature rupture of membranes.

Neurologic manifestations / development. Muscular hypotonia with muscular weakness is common; weakness may be severe with wrist drop and may lead to upper brachial plexus palsy.

Mild-to-moderate gross motor delay is common. Walking nearly always occurs before age two years. Loss of motor milestones does not occur. Fine motor skills can be affected as well due to weakness and/or joint laxity. Intellect is unaffected.

Musculoskeletal manifestations. Generalized joint hypermobility is present in neonates. Recurrent joint dislocations are a common serious problem. The joints most affected include hips, shoulders, knees, and wrists.

Thoracic (kypho)scoliosis is also common in the neonate. Kyphoscoliosis appears during infancy and becomes moderate to severe in childhood.

Clubfoot (talipes equinovarus) deformities are present at birth in approximately 25% of affected individuals. Pectus deformity is also present with similar frequency.

Osteopenia/osteoporosis occurs in 25% of affected individuals, but its clinical significance is currently unknown.

A marfanoid habitus is often striking, including pectus deformity (~25%), long limbs, and arachnodactyly.

Skin. All individuals with *PLOD1*-kEDS have hyperelastic and easily stretched skin with velvety texture. The skin is friable with poor wound healing. An estimated 60% of individuals have widened atrophic scarring. Bruising occurs easily in all individuals, and severe bruising occurs in approximately 50%.

Cardiovascular. Both aortic dilatation/dissection and rupture of medium-sized arteries may occur. The rate of progression of aortic root dilatation in *PLOD1*-kEDS is not known. Mitral valve prolapse is common. Venous ectasia following use of intravenous catheters has been reported [Heim et al 1998]. Antenatal/neonatal brain hemorrhage has been described [Giunta et al 2005b, Rohrbach et al 2011, Tosun et al 2014, Quade et al 2017, Ni et al 2020, Shin et al 2020, Yan et al 2022].

Eyes. Bluish sclerae and refractive errors (high myopia, hypermetropia) are common. Many individuals have microcornea, although its clinical significance is unclear. Ocular fragility (scleral as opposed to corneal), which was observed in the original reports of individuals with procollagen lysyl hydroxylase deficiency [Pinnell et al 1972], is found in a minority of individuals.

Hernias. An equal distribution of umbilical and inguinal hernias is reported.

Other. High palate is also reported.

Prognosis. Life span may be normal. Adults with severe kyphoscoliosis are at risk for complications from restrictive lung disease, recurrent pneumonia, and cardiac failure. Vascular rupture is the major life-threatening complication in this disorder.

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been reported to date.

Penetrance

Penetrance for *PLOD1*-kEDS is 100%.

Nomenclature

Kyphoscoliotic EDS (or EDS, kyphoscoliotic form) was initially referred to as EDS, oculoscoliotic form after its first description by Pinnell et al [1972].

Prior to the development of the 1998 Villefranche classification, kEDS was known as Ehlers-Danlos syndrome type VI (EDS VI) or Ehlers-Danlos syndrome type VIA (EDS VIA).

Giunta et al [2005a] convincingly demonstrated that Nevo syndrome is part of the spectrum of EDS VI; thus, the term "Nevo syndrome" does not refer to a distinct disorder but is now incorporated into kEDS.

In 2017, the International EDS Consortium proposed a revised EDS classification system. The new nomenclature for EDS, kyphoscoliotic form is kyphoscoliotic EDS, or kEDS [Malfait et al 2017].

Prevalence

PLOD1-kEDS is rare; the exact prevalence is unknown. A disease incidence of approximately 1:100,000 live births is a reasonable estimate.

Prevalence does not vary by race or ethnicity, although many of the reported and unreported individuals originated from Turkey, the Middle East, and Greece [Giunta et al 2005a, Giunta et al 2005b].

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *PLOD1*.

Differential Diagnosis

PLOD1-related kyphoscoliotic Ehlers-Danlos syndrome (*PLOD1*-kEDS) has some overlapping clinical features with other forms of Ehlers-Danlos syndrome (EDS), particularly classic EDS and vascular EDS. Abnormal wound healing and joint laxity are present in many EDS types. Although all types of EDS involve a relatively high risk for scoliosis compared to the general population, scoliosis in *PLOD1*-kEDS is usually more severe and of earlier onset than that seen in other EDS types.

Table 3 lists selected EDS-related genes and other genes of interest in the differential diagnosis of *PLOD1*-kEDS. Of note, all of the disorders in Table 3 can be biochemically distinguished from *PLOD1*-kEDS by normal lysyl hydroxylase enzyme activity as indicated by the absence of a markedly increased ratio of deoxypyridinoline to pyridinoline cross-links in urine.

Table 3. Selected Genes of Interest in the Differential Diagnosis of *PLOD1*-Related Kyphoscoliotic Ehlers-Danlos Syndrome

Gene	Disorder	MOI	Clinical Features of Disorder	
			Overlapping w/*PLOD1*-kEDS	Distinguishing from *PLOD1*-kEDS
Other forms of Ehlers-Danlos syndrome (EDS)				
AEBP1	Classical-like EDS type 2 (OMIM 618000)	AR	• Atrophic scarring, easy bruising • Joint hypermobility • Skin hyperextensibility	• Prematurely aged appearance • Thinning of hair or (partial) alopecia
B3GALT6 *B4GALT7* *SLC39A13*	Spondylodysplastic EDS (spEDS) (OMIM 130070, 612350, 615349)	AR	• Joint hypermobility • Poor wound healing • Hypotonia • Skin hyperextensibility	Variable by related gene: • Progeroid characteristics • Vertebral dysplasia w/ moderate short stature & characteristic features of the hands (thenar atrophy, short metacarpals & phalanges, inability to adduct thumbs)
CHST14 *DSE*	Musculocontractural EDS (OMIM 601776, 615539)	AR	• Blue sclerae • Marfanoid habitus • Generalized joint hypermobility • Scoliosis • Skin hyperextensibility • Easy bruising; atrophic scarring • Hypotonia • Refractive errors	• Characteristic facies • Adducted thumbs & feet [1] • Gastrointestinal & genitourinary manifestations
COL3A1 (*COL1A1*) [2]	Vascular EDS (vEDS)	AD [3]	Vascular rupture (may be a feature of *PLOD1*-kEDS)	• Intestinal rupture • Uterine rupture during pregnancy
COL5A1 *COL5A2* (*COL1A1*) [4]	Classic EDS (cEDS)	AD	• Atrophic scarring, easy bruising • Joint hypermobility • Skin hyperextensibility	• Absence of congenital muscular hypotonia • Scoliosis rather than kyphoscoliosis

Table 3. continued from previous page.

Gene	Disorder	MOI	Clinical Features of Disorder	
			Overlapping w/*PLOD1*-kEDS	Distinguishing from *PLOD1*-kEDS
FKBP14	*FKBP14*-kEDS	AR	• Congenital muscular hypotonia • Congenital/early-onset kyphoscoliosis • Generalized joint hypermobility	• Myopathy • Hearing loss
TNXB	*TNXB*-related classical-like EDS (clEDS)	AR	• Easy bruising • Joint hypermobility • Skin hyperextensibility, velvety skin	Absence of atrophic scarring & kyphoscoliosis
Other disorders				
PRDM5 *ZNF469*	Brittle cornea syndrome (OMIM PS229200)	AR	• Corneal disorder • Skin hyperelasticity • Joint hypermobility	• Thinning of cornea w/risk of rupture • Deafness (mixed conductive & sensorineural)

AD = autosomal dominant; AR = autosomal recessive; EDS = Ehlers-Danlos syndrome; MOI = mode of inheritance
1. Malfait et al [2010], Janecke et al [2016]
2. Pathogenic variants in *COL1A1* are listed as a rare cause of vEDS in the 2017 International Classification of the Ehlers-Danlos Syndromes [Malfait et al 2017].
3. Vascular EDS is almost always inherited in an autosomal dominant manner, but rare examples of biallelic inheritance have been reported.
4. The proportion of cEDS attributed to pathogenic variants in *COL5A1* is 75%-78%; in *COL5A2*, 14%; and in *COL1A1*, <1%. The associated gene is unknown in ≤10% of individuals with cEDS.

Congenital myopathies. Most congenital myopathies present with poor muscle tone and increased range of motion of small and large joints. Joint laxity can be difficult to distinguish from muscular hypotonia, particularly in infants and children. In *PLOD1*-kEDS, in which both hypotonia and joint laxity are present, the increased range of motion is often striking. Velvety skin texture may help distinguish *PLOD1*-kEDS from congenital myopathies such as X-linked myotubular myopathy. Unlike spinal muscular atrophy, *PLOD1*-kEDS is characterized by normal deep tendon reflexes.

Disorders with early-onset hypotonia. Many syndromic and metabolic disorders include early-onset hypotonia. In these disorders, however, the other manifestations of *PLOD1*-kEDS are generally absent, and additional features are usually present.

Management

No clinical practice guidelines for *PLOD1*-related kyphoscoliotic Ehlers-Danlos syndrome (*PLOD1*-kEDS) have been published.

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *PLOD1*-kEDS, the evaluations summarized in Table 4 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 4. *PLOD1*-Related Kyphoscoliotic Ehlers-Danlos Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Neuromuscular	PT eval to develop plan for ongoing therapy to strengthen large muscle groups & prevent recurrent shoulder dislocation	

Table 4. continued from previous page.

System/Concern	Evaluation	Comment
Musculoskeletal	Eval for kyphoscoliosis incl photographs & radiographs	Documentation is recommended in view of progressive kyphoscoliosis.
	Referral to orthopedics for those w/clubfoot	
Skin	Consultation w/dermatologist to review skin findings & discuss treatment of abnormal wound healing	
Cardiovascular	Measurement of aortic root size & assessment of heart valves by echocardiogram	At diagnosis or by age 5 yrs
	Visualization of entire aorta w/CT or MRA	By young adulthood, or earlier if aortic or arterial dilatation is identified on echocardiogram
Eyes	Formal ophthalmologic eval for myopia, astigmatism, & retinal detachment	
Hernia	Referral to surgery for those needing hernia repair	
Genetic counseling	By genetics professionals [1]	To obtain a pedigree & inform affected persons & their families re nature, MOI, & implications of *PLOD1*-kEDS to facilitate medical & personal decision making

MOI = mode of inheritance; MRA = magnetic resonance angiogram; *PLOD1*-kEDS = *PLOD1*-related kyphoscoliotic Ehlers-Danlos syndrome; PT = physical therapy
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

There is no cure for *PLOD1*-kEDS. 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 5).

Table 5. *PLOD1*-Related Kyphoscoliotic Ehlers-Danlos Syndrome: Treatment of Manifestations

Manifestation/Concern	Treatment	Considerations/Other
Neuromuscular	• PT for older children, adolescents, & adults to strengthen large muscle groups, particularly at the shoulder girdle, & to prevent recurrent shoulder dislocation • Swimming is recommended.	
Musculoskeletal	• Referral to orthopedic surgeon for mgmt of kyphoscoliosis • Bracing may be required to support unstable joints.	Orthopedic surgery is not contraindicated in persons w/ *PLOD1*-kEDS & can be performed as necessary.
Skin	• Due to skin fragility, protective pads over knees, shins, & elbows may prevent lacerations, particularly in children. • Use of helmets for active sports • Close dermal wounds w/o tension, preferably in 2 layers. • Apply deep stitches generously. • Leave cutaneous stitches in place twice as long as usual, & additional fixation of adjacent skin w/adhesive tape can help prevent stretching of the scar.	

Table 5. continued from previous page.

Manifestation/Concern	Treatment	Considerations/Other
Cardiovascular	• Treatment per cardiologist • Vigilant observation & control of blood pressure can ↓ risk of arterial rupture. • Those w/aortic dilatation may require treatment w/beta-blockers to prevent further expansion. • Those w/mitral valve prolapse should follow standard AHA guidelines for antimicrobial prophylaxis.	Vascular surgery is fraught w/ danger. While virtually no surgical literature exists on *PLOD1*-kEDS, see Freeman et al [1996] for review of similar surgical complications reported in vascular EDS.
Ophthalmologic	• Corrective lenses for myopia &/or astigmatism • Laser treatment of retina in those w/imminent detachment	
Hernia	Careful stitching is required for hernia repair.	

AHA = American Heart Association; EDS = Ehlers-Danlos syndrome; *PLOD1*-kEDS = *PLOD1*-related kyphoscoliotic Ehlers-Danlos syndrome; PT = physical therapy

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 6 are recommended.

Table 6. *PLOD1*-Related Kyphoscoliotic Ehlers-Danlos Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Neuromuscular	PT assessment for weakness & motor issues	Annually or more frequently as needed
Musculoskeletal	Orthopedics assessment for kyphoscoliosis & recurrent dislocations	
	Assessment for osteopenia per orthopedist	As needed beginning at age 10-12 yrs
Respiratory	Assessment for respiratory complications due to severe kyphoscoliosis per pulmonologist	As needed in those w/severe kyphoscoliosis
Cardiovascular	• Assessment w/cardiologist • Echocardiogram	Every 5 yrs beginning at age 5 yrs, or as recommended by cardiologist
	CT or MRA for medium-sized arteries & entire aorta	Consider intermittently beginning in young adults & at least annually in those w/aortic or arterial dilatation
	Monitor blood pressure.	Per cardiologist
Ophthalmologic	Ophthalmologic exam for mgmt of myopia & early detection of glaucoma or retinal detachment	Annually
Hernia	Exam for inguinal hernia	Annually or as needed

MRA = magnetic resonance angiogram; PT = physical therapy

Agents/Circumstances to Avoid

In children with significant joint hyperextensibility, sports that place stress on the joints (e.g., gymnastics, long-distance running) should be avoided.

High-impact sports (collision sports), heavy lifting, and weight training with extreme lifting should be avoided.

Arteriography should be discouraged and used only to identify life-threatening sources of bleeding prior to surgical intervention because of the risk of vascular injury.

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger sibs of a proband in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures. Evaluations can include:

- Molecular genetic testing if both *PLOD1* pathogenic variants have been identified in the proband;
- Measurement of cross-links in urine for markedly increased ratio of deoxypyridinoline to pyridinoline by high-performance liquid chromatography if only one or no pathogenic variant in *PLOD1* has been identified in the proband and the diagnosis in the proband was established with biochemical testing. (Note: Carrier status cannot be reliably ascertained by biochemical testing or by enzyme assay.)

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

Pregnancy Management

Affected pregnant women may be at increased risk for miscarriage, premature rupture of membranes, and rupture of arteries [Esaka et al 2009]. Two affected women had a total of seven pregnancies resulting in three miscarriages and four healthy children, three of whom were born vaginally at term and one of whom was born at 24 weeks; there were no maternal complications [B Steinmann, unpublished data]. Monitoring aortic root measurement during pregnancy by echocardiogram is recommended. Delivery should be performed in a medical center with a high-risk perinatologist in attendance.

Therapies Under Investigation

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

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

PLOD1-related kyphoscoliotic Ehlers-Danlos syndrome (*PLOD1*-kEDS) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for a *PLOD1* pathogenic variant.
- If both *PLOD1* pathogenic variants have been identified in the proband, molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for a *PLOD1* 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.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for a *PLOD1* pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. The offspring of an individual with *PLOD1*-kEDS are obligate heterozygotes (carriers).

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *PLOD1* pathogenic variant.

Carrier Detection

Molecular genetic testing. Carrier testing for at-risk relatives requires prior identification of the *PLOD1* pathogenic variants in the family.

Biochemical testing. Although carriers do tend to have a slightly elevated ratio of deoxypyridinoline (Dpyr) to pyridinoline (Pyr) cross-links in urine [Kraenzlin et al 2008], carrier status cannot be reliably ascertained by biochemical testing or enzyme assay.

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, are carriers, or are at risk of being carriers.
- Affected pregnant women may be at increased risk for miscarriage, premature rupture of membranes, and rupture of arteries (see Pregnancy Management).

Prenatal Testing and Preimplantation Genetic Testing

Once the *PLOD1* pathogenic variants have been identified in an affected family member, molecular genetic prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal 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.

- **Ehlers-Danlos Society - Europe**
  United Kingdom
  Phone: +44 203 887 6132
- **Ehlers-Danlos Support UK**
  United Kingdom
  Phone: 0208 736 5604; 0800 9078518
  www.ehlers-danlos.org
- **The Ehlers-Danlos Society**
  Phone: 410-670-7577
  www.ehlers-danlos.com
- **MedlinePlus**
  Ehlers-Danlos Syndrome
- **DICE EDS and HSD Global Registry**
  www.ehlers-danlos.com/eds-global-registry

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. PLOD1-Related Kyphoscoliotic Ehlers-Danlos Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
PLOD1	1p36.22	Procollagen-lysine,2-oxoglutarate 5-dioxygenase 1	PLOD1 @ LOVD	PLOD1	PLOD1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for PLOD1-Related Kyphoscoliotic Ehlers-Danlos Syndrome (View All in OMIM)

153454	PROCOLLAGEN-LYSINE, 2-OXOGLUTARATE 5-DIOXYGENASE; PLOD1
225400	EHLERS-DANLOS SYNDROME, KYPHOSCOLIOTIC TYPE, 1; EDSKSCL1

Molecular Pathogenesis

PLOD1 encodes procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1 (PLOD1; also called lysyl hydroxylase, or LH1). This enzyme hydroxylates lysyl residues in -Xaa-Lys-Gly- collagen sequences, which serve as sites of attachment for carbohydrate units and play an essential role in the formation of intra- and intermolecular collagen cross-links. Lack of PLOD1 leads to decreased hydroxylation and glycosylation of lysine-amino residues in collagen, resulting in compromised formation of collagen cross-links and subsequent mechanical instability in the tissues affected.

Mechanism of disease causation. Loss of function. Western blot analysis using polyclonal antibody to recombinant PLOD1 showed decreased levels of PLOD1 in two individuals with *PLOD1*-related kyphoscoliotic Ehlers-Danlos syndrome [Walker et al 2004].

***PLOD1*-specific laboratory technical considerations.** A common pathogenic variant, a duplication of exons 10-16, is caused by a homologous recombination event between identical 44-bp Alu sequences in introns 9 and 16 [Pousi et al 1994]. *PLOD1* testing should include analysis for this duplication.

Table 7. *PLOD1* Pathogenic Variants Referenced in This *GeneReview*

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
NM_000302.3	8.9-kb duplication of exons 10-16 [1]	--	Most common pathogenic variant; allele frequency was 30% in probands from 73 families [Yeowell et al 2005, Brady et al 2017].
NM_000302.3 NP_000293.2	c.955C>T	p.Arg319Ter	Common variant in Arab population [Brady et al 2017]
	c.1533C>G	p.Tyr511Ter	Third most common pathogenic variant [Brady et al 2017]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.
GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Chapter Notes

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Revision History

- 13 June 2024 (sw) Comprehensive update posted live
- 12 April 2018 (ha) Comprehensive update posted live
- 24 January 2013 (me) Comprehensive update posted live
- 19 February 2008 (me) Comprehensive update posted live
- 12 July 2005 (me) Comprehensive update posted live
- 12 March 2003 (me) Comprehensive update posted live
- 2 February 2000 (me) Review posted live
- 7 April 1999 (rw) Original submission

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