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PLOD1-Related Kyphoscoliotic Ehlers-Danlos Syndrome

Synonyms: EDS, Kyphoscoliotic Form; EDS Type VI; EDS VI; Ehlers-Danlos Syndrome Type VI; kEDS; Lysyl-Hydroxylase Deficiency

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Summary

Clinical characteristics

PLOD1-related kyphoscoliotic Ehlers-Danlos syndrome (kEDS) is an autosomal recessive generalized connective tissue disorder characterized by hypotonia, early-onset kyphoscoliosis, and generalized joint hypermobility in association with skin fragility and ocular abnormality. Intelligence is normal. Life span may be normal, but affected individuals are at risk for rupture 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*-related kEDS is established in a proband with typical clinical findings and biallelic pathogenic (or likely pathogenic) variants in *PLOD1* identified by molecular genetic testing. If only one or no pathogenic variant is identified, testing for a markedly increased ratio of deoxypyridinoline to pyridinoline crosslinks in urine measured by high-performance liquid chromatography (HPLC) (a highly sensitive, specific, and inexpensive test) may be necessary for confirmation of the diagnosis.

Management

Treatment of manifestations: Management of kyphoscoliosis by an orthopedic surgeon, including surgery as needed; physical therapy to strengthen large muscle groups; bracing to support unstable joints; protective pads and helmets during active sports; control of blood pressure to reduce the risk for arterial rupture; treatment with beta-blockers as needed to prevent aortic dilatation.

Prevention of secondary complications: Standard American Heart Association guidelines for antimicrobial prophylaxis for mitral valve prolapse.

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Surveillance: Regular follow up by an orthopedic surgeon for management of kyphoscoliosis; routine examination for inguinal hernia; routine ophthalmologic examination for management of myopia and early detection of glaucoma or retinal detachment; echocardiogram at five-year intervals even if the initial echocardiogram is normal.

Agents/circumstances to avoid: Sports that stress the joints, such as gymnastics or long-distance running; high-impact sports for eye injury concerns.

Pregnancy management: Affected pregnant women may be at increased risk for miscarriage, premature rupture of membranes, and rupture of arteries.

Genetic counseling

PLOD1-related kEDS is inherited in an autosomal recessive manner. At conception, each sib of a proband with EDS, kyphoscoliotic form has 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. Once the *PLOD1* pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

PLOD1-related kyphoscoliotic Ehlers-Danlos syndrome (kEDS) is an autosomal recessive generalized connective tissue disorder characterized by hypotonia, early-onset kyphoscoliosis, generalized joint hypermobility, skin fragility, and ocular abnormality. Pathogenic variants in *PLOD1* cause abnormal collagen biosynthesis resulting in decreased lysyl hydroxylase enzyme activity.

A disorder with a clinically overlapping phenotype known as *FKBP14*-related kEDS (not addressed in this *GeneReview*) is distinguished by the presence of myopathy and hearing loss, normal lysyl hydroxylase enzyme activity, and pathogenic variants in *FKBP14*; see Differential Diagnosis and *FKBP14*-Related Kyphoscoliotic EDS.

Suggestive Findings

PLOD1-related kyphoscoliotic Ehlers-Danlos syndrome (kEDS) **should be suspected** in individuals with the following findings (adapted from Malfait et al [2017]):

Major criteria

- Congenital muscular hypotonia (progressive or non-progressive congenital or early-onset kyphoscoliosis)
- 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*-related kEDS

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

Establishing the Diagnosis

The diagnosis of *PLOD1*-related kEDS **is established** in a proband with typical clinical findings and biallelic pathogenic (or likely pathogenic) variants in *PLOD1* identified by molecular genetic testing (see Table 1). If only one or no pathogenic variant is 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 section 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, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of *PLOD1*-related kEDS is broad, individuals with the distinctive findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited generalized connective tissue disorders are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

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

- **Single-gene testing.** Sequence analysis of *PLOD1* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Gene-targeted deletion/duplication analysis is used to detect intragenic deletions or duplications.

  Note: A common intragenic duplication caused by an Alu-Alu recombination in introns 9 and 16 accounts for approximately 30% (42/139) of disease alleles [Yeowell et al 2005, 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 alleles 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. 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*; thus, clinicians need to determine which multigene panel is most likely 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. (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 (see Table 1).

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** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

Exome array (when clinically available) may be considered if exome sequencing is non-diagnostic.

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] Detectable by Method
PLOD1	Sequence analysis [3]	67% [4]
	Gene-targeted deletion/duplication analysis [5]	33% [6]

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 small intragenic deletions/insertions and missense, nonsense, and splice site variants; 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. 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.
6. Pousi et al [1994], Pousi et al [1998], Yeowell et al [2000], Giunta et al [2005b]

Additional Confirmatory Testing

Biochemical testing. Deficiency of the enzyme procollagen-lysine, 2-oxoglutarate 5 dioxygenase-1 (PLOD1) 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*-related kEDS. The normal ratio of Dpyr:Pyr cross-links is approximately 0.2, whereas in kyphoscoliotic EDS the ratio is approximately 6.0 [Steinmann et al 1995, Al-Hussain et al 2004]. 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

A range of clinical severity is observed in individuals with *PLOD1*-related kyphoscoliotic Ehlers-Danlos syndrome (kEDS) for each of the systems discussed in this section [Steinmann et al 2002, Rohrbach et al 2011, Brady et al 2017].

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

Musculoskeletal

- Muscular hypotonia with joint laxity is present in neonates.
- Muscular weakness is common, may be severe with wrist drop, and may lead to upper brachial plexus palsy.
- Gross motor delay (mild to moderate) is common.
  - Walking nearly always occurs before age two years.
  - Loss of motor milestones does not occur.
- Intellect is unaffected.
- A marfanoid habitus is often striking.
- Thoracic scoliosis is common in the neonate. The kyphoscoliosis appears during infancy and becomes moderate to severe in childhood. Adults with severe kyphoscoliosis are at risk for complications from restrictive lung disease, recurrent pneumonia, and cardiac failure.
- Clubfoot (equinovarus) deformities are present at birth in approximately 30% of affected individuals.
- Recurrent joint dislocations (associated with generalized joint hypermobility) are a common serious problem.
- Osteopenia/osteoporosis occurs in all individuals, but its clinical significance is currently unknown.

Skin

- All individuals with *PLOD1*-related kEDS have hyperelastic and easily stretched skin.
- An estimated 60% of individuals have abnormal scarring, characterized by thinness and widening.
- Bruising occurs easily in all individuals, and severe bruising occurs in approximately 50%.
- An equal distribution of umbilical and inguinal hernias was reported in 12 affected individuals.

Eyes

- 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.
- Bluish sclerae are a common feature.
- High myopia is common.
- Many individuals have microcornea, although its clinical significance is unclear.
- Glaucoma and retinal detachment also occur.

Cardiovascular

- Vascular rupture is the major life-threatening complication in this disorder. Both aortic dilatation/dissection and rupture of medium-sized arteries may occur. The rate of progression of aortic root dilatation in *PLOD1*-related kEDS is not known.
- Mitral valve prolapse is common.
- Venous ectasia following use of intravenous catheters has been reported [Heim et al 1998].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have been reported to date.

Penetrance

Penetrance for *PLOD1*-related kEDS is 100%.

Nomenclature

Kyphoscoliotic EDS (kEDS) 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 EDS VI (or 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-related 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 cases originated in Turkey, the Middle East, and Greece [Giunta et al 2005a, Giunta et al 2005b].

Carrier frequency is estimated at 1:150.

Genetically Related (Allelic) Disorders

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

Differential Diagnosis

Other forms of Ehlers-Danlos syndrome. Kyphoscoliotic Ehlers-Danlos syndrome (kEDS) has some overlapping clinical features with other forms of 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 kEDS is usually more severe and of earlier onset than that seen in other EDS types.

The diagnosis of *PLOD1*-related kEDS can be confirmed by molecular genetic testing of *PLOD1* or biochemical analysis of urinary Dpyr/Pyr cross-links.

Several rare conditions share features of *PLOD1*-related kEDS but have normal lysyl hydroxylase enzyme activity as indicated by results of the urinary Dpyr/Pyr testing. These include:

- EDS with progressive kyphoscoliosis, myopathy, and sensorineural hearing loss caused by biallelic pathogenic variants in *FKBP14* (encoding the collagen-specific chaperone peptidyl-prolyl *cis-trans* isomerase FKBP14 [alias: FKBP22]) [Baumann et al 2012, Brady et al 2017, Giunta et al 2018]. This condition, described in 26 individuals to date, is classified as kEDS-*FKBP14* in the 2017 International

Classification of the Ehlers-Danlos Syndromes [Malfait et al 2017]. See *FKBP14*-Related Kyphoscoliotic EDS.

- Musculocontractural EDS (mcEDS; originally EDS VIB), caused by biallelic pathogenic variants in *CHST14* (encoding carbohydrate sulfotransferase 14) or *DSE* (encoding dermatan-sulfate epimerase) and characterized by additional clinical findings including adducted thumbs and feet [Malfait et al 2010, Janecke et al 2016]
- Spondylocheirodysplastic EDS (spEDS; originally EDS VIC), including:
  - Conditions with additional progeroid characteristics caused by biallelic pathogenic variants in the galactosyl-related genes *B4GALT7* and *B3GALT6*;
  - Conditions with additional clinical findings including signs of skeletal dysplasia (*spondylo*) with moderate short stature and characteristic features of the hands (thenar atrophy, *cheiro*) caused by biallelic pathogenic variants in *SLC39A13*, the zinc transporter gene; the urinary excretion of pyridinolines is changed to a Dpyr/Pyr ratio of approximately 1.0, falling between the ratio in controls and in kEDS [Giunta et al 2008].

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 kEDS, in which both hypotonia and joint laxity are present, the increased range of motion is often striking. Velvety skin texture may help distinguish kEDS from congenital myopathies such as X-linked myotubular myopathy. Unlike spinal muscular atrophy, kEDS is characterized by normal deep tendon reflexes.

Corneal disorder. Brittle cornea syndrome (BCS) is associated with corneal rupture following minor trauma (OMIM 229200 and 614170). Although this disorder is also characterized by skin hyperelasticity and joint hypermobility, biochemical analysis reveals normal ratios of urinary pyridinolines and lysyl hydroxylase enzyme activity [Al-Hussain et al 2004]. BCS is caused by biallelic pathogenic variants in *ZNF469* or *PRDM5*.

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

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with *PLOD1*-related kyphoscoliotic Ehlers-Danlos syndrome (kEDS) the following evaluations are recommended if not already completed:

- **Musculoskeletal**
  - Evaluation for kyphoscoliosis. Photographic and radiologic documentation of the spine is recommended in view of the progressive kyphoscoliosis.
  - Physical therapy evaluation to develop a plan for ongoing therapy to strengthen large muscle groups and prevent recurrent shoulder dislocation
- **Skin.** Consultation with a dermatologist to review skin findings and discuss treatment of abnormal wound healing.
- **Ophthalmologic.** Formal ophthalmologic evaluation at diagnosis for myopia, astigmatism, and retinal detachment
- **Cardiovascular.** Measurement of aortic root size and assessment of heart valves by echocardiogram at the time of diagnosis or by age five years
- **Other.** Consultation with a clinical geneticist and/or genetic counselor

Treatment of Manifestations

Musculoskeletal

- Refer to an orthopedic surgeon for management of kyphoscoliosis.
- Orthopedic surgery is not contraindicated in individuals with *PLOD1*-related kEDS and can be performed as necessary.
- Bracing may be required to support unstable joints.
- Physical therapy is recommended for older children, adolescents, and adults to strengthen large muscle groups, particularly at the shoulder girdle, and to prevent recurrent shoulder dislocation. Swimming is recommended.

Skin

- Due to skin fragility, protective pads over knees, shins, and elbows may be helpful in preventing lacerations, particularly in children.
- The use of helmets in active sports is always advised.

Ophthalmologic

- Myopia and/or astigmatism may be corrected by glasses or contact lenses.
- Laser treatment of the retina is indicated in case of imminent detachment.

Cardiovascular

- Regular monitoring by a cardiologist
- Vigilant observation and control of blood pressure can reduce the risk of arterial rupture.
- Vascular surgery is fraught with danger. While virtually no surgical literature exists on *PLOD1*-related kEDS, the review by Freeman et al [1996] on surgical complications of vascular EDS is relevant.
- Individuals with aortic dilatation may require treatment with beta-blockers to prevent further expansion.

Prevention of Secondary Complications

Individuals with mitral valve prolapse should follow standard American Heart Association guidelines for antimicrobial prophylaxis.

Surveillance

The following are appropriate:

- Regular follow up by an orthopedic surgeon for management of kyphoscoliosis
- Routine examination for inguinal hernia and surgical referral as necessary
- Routine ophthalmologic examination for management of myopia and early detection of glaucoma or retinal detachment
- Regular follow up by a cardiologist to monitor the echocardiogram at five-year intervals, even if the initial echocardiogram is normal
- Vigilant observation and control of blood pressure to decrease the risk of arterial rupture

Females should be made aware of complications associated with pregnancy (see Pregnancy Management).

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 should be avoided for eye injury concerns.

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger sibs of a proband / at-risk relatives in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures.

Such an evaluation includes molecular genetic testing if the pathogenic variants in the family are known.

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 [Steinmann, unpublished]. 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 (kEDS) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are obligate heterozygotes (i.e., carriers of one *PLOD1* pathogenic variant).
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- At conception, each sib of an affected individual has 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 affected individual with *PLOD1*-related kyphoscoliotic EDS 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 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 genetic testing. Although carriers do tend to have slightly elevated urinary Dpyr/Pyr ratios [Kraenzlin et al 2008], carrier status cannot be reliably ascertained by biochemical testing or by 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, clarification of carrier status, 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.

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Once the *PLOD1* pathogenic variants 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 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

Gene structure. *PLOD1* is approximately 40 kb and consists of 19 exons with an unusually large (12.5-kb) first intron. The introns are of high homology, generating many potential recombination sites within the gene. For a detailed summary of gene and protein information, see Table A, **Gene**.

Pathogenic variants. More than 39 different pathogenic variants in *PLOD1* have been associated with kyphoscoliotic EDS (kEDS) [Yeowell & Walker 2000, Giunta et al 2005b, Walker et al 2005, Brady et al 2017]. These variants are located throughout the gene.

- The most common pathogenic variant, an 8.9-kb duplication of seven exons (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]. The allele frequency of the duplication was 30% in probands with kEDS from 73 families [Yeowell et al 2005, Brady et al 2017]. Intragenic deletions are also reported.
- Nine affected individuals from six families, all of Arab descent, are homozygous for nonsense variant p.Arg319Ter, giving an allelic frequency of 13% [Brady et al 2017].
- The third most common pathogenic variant in *PLOD1* is p.Tyr511Ter. The allele frequency of this variant in probands with kEDS is 5% [Brady et al 2017].

The first and third pathogenic variants have been linked by haplotype analysis to a common ancestral gene [Yeowell & Walker 2000].

Table 2. *PLOD1* Pathogenic Variants Referenced in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
8.9-kb duplication of exons 10-16 [1]	--	NM_000302.3

Table 2. continued from previous page.

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.955C>T	p.Arg319Ter	NM_000302.3 NP_000293.2
c.1533C>G	p.Tyr511Ter	

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.
1. Not standard nomenclature

Normal gene product. The cDNA for *PLOD1* codes for a polypeptide of 727 amino acids, including a signal peptide of 18 residues. Lysyl hydroxylase 1 (LH1) exists as a dimer of identical subunits of molecular weight approximately 80-85 kd, depending on the state of glycosylation. The enzyme requires Fe^{2+}, α-ketoglutarate, O_2, and ascorbate as cofactors. The C-terminal region is well conserved across species and is thought to contain the active site of the enzyme [Yeowell 2002].

Abnormal gene product. Western blot analysis using polyclonal antibody to recombinant LH1 showed decreased levels of LH1 in two individuals with *PLOD1*-related kEDS [Walker et al 2004].

Chapter Notes

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