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Classic Ehlers-Danlos Syndrome

Synonyms: Classical Ehlers-Danlos Syndrome; Ehlers-Danlos Syndrome, Classical Type; cEDS

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Summary

Clinical characteristics

Classic Ehlers-Danlos syndrome (cEDS) is a heritable connective tissue disorder characterized by skin hyperextensibility, atrophic scarring, and generalized joint hypermobility (GJH). The skin is soft, velvety, or doughy to the touch. In addition, the skin is hyperextensible, meaning that it extends easily and snaps back after release. The skin is fragile, as manifested by splitting of the dermis following relatively minor trauma, especially over pressure points (knees, elbows) and areas prone to trauma (shins, forehead, chin). Wound healing is poor, and stretching, thinning, and pigmentation of scars is characteristic, leading to the presence of atrophic and/or hemosiderotic scars. Easy bruising is also a hallmark of cEDS. GJH is present in most but not all affected individuals, evidenced by the presence of a Beighton score of five or greater, either on examination or historically. Joint instability complications may comprise sprains and dislocations/subluxations. Mild muscle hypotonia with delayed motor development, fatigue and muscle cramps, and some skeletal morphologic alterations (scoliosis, pectus deformities, genus/hallux valgus, pes planus) are regularly observed. While aortic root dilatation and mitral valve prolapse are seen in cEDS, they are rarely clinically significant. Arterial aneurysm and rupture have been reported in a few individuals with cEDS.

Diagnosis/testing

The diagnosis of cEDS is established in a proband with characteristic clinical features and a heterozygous pathogenic variant in *COL1A1*, *COL5A1*, or *COL5A2* identified by molecular genetic testing.

Management

Treatment of manifestations: Dermal wounds are closed without tension, preferably in two layers. For other wounds, deep stitches are applied generously; cutaneous stitches are left in place twice as long as usual; and the borders of adjacent skin are carefully taped to prevent stretching of the scar. Young children with skin fragility can wear pads or bandages over the forehead, knees, and shins to avoid skin tears. Older children can wear soccer pads or ski stockings with shin padding during activities. Braces as needed to improve joint stability;

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referral to orthopedist, rheumatologist, or physical therapist and occupational therapist as needed. Mobility devices as needed. Adjust sleep surface as needed to improve sleep quality and decrease pain. Those with hypotonia, joint instability, and chronic pain may need to adapt lifestyles accordingly. Anti-inflammatory drugs may alleviate joint pain. Children with hypotonia and delayed motor development benefit from physiotherapy. Non-weight-bearing exercise promotes muscle strength and coordination. Ascorbic acid (vitamin C) may reduce bruising. DDAVP® (desmopressin) may be useful to normalize bleeding time. Cardiovascular manifestations are treated in a standard manner.

Surveillance: Assess for skin fragility, joint instability, occupational and physical therapy needs, mobility issues, and pain at each visit or as needed. Evaluation for hypotonia and motor development at each visit in infants and children. Assess for easy bruising and/or prolonged bleeding at each visit. Evaluation of clotting factors if severe easy bruising is present. Yearly echocardiogram when aortic dilatation and/or mitral valve prolapse are present.

Agents/circumstances to avoid: Sports with heavy joint strain.

Genetic counseling

Classic EDS is inherited in an autosomal dominant manner. Approximately 50% of individuals diagnosed with cEDS have an affected parent; approximately 50% of individuals diagnosed with cEDS have the disorder as the result of a *de novo* pathogenic variant. Each child of an individual with cEDS has a 50% chance of inheriting the pathogenic variant. Once the cEDS-related pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

Diagnosis

There are no consensus clinical diagnostic criteria for classic Ehlers-Danlos syndrome (cEDS); diagnosis requires molecular testing.

Suggestive Findings

Classic EDS should be suspected in a proband with either of the following:

- Major criteria skin hyperextensibility and atrophic scarring
  OR
- Major criterion generalized joint hypermobility (GJH) and/or ≥3 minor criteria

Major criteria

- **Skin hyperextensibility** (see Figure 1) is measured by pinching and lifting the cutaneous and subcutaneous layers of the skin on the volar surface at the middle of the nondominant forearm as described by Remvig et al [2009]. Skin is hyperextensible if it can be stretched over a standardized cutoff in three of the following areas: 1.5 cm for the distal part of the forearms and the dorsum of the hands; 3 cm for neck, elbows, and knees.
- **Atrophic scarring** (See Figure 2.)
- **GJH** (see Figure 3) depends on an individual's age, sex, and family and ethnic background. Joint hypermobility in cEDS is usually general, affecting both large and small joints, and is usually noted when a child starts to walk. It should be assessed using the Beighton scale, the most widely accepted grading system for the objective semiquantification of joint hypermobility (see Table 1). A Beighton score of ≥5 is considered positive for the presence of GJH.

Table 1. Beighton Criteria for Joint Hypermobility

Joint/Finding	Negative	Unilateral	Bilateral
Passive dorsiflexion of the 5th finger >90°	0	1	2
Passive flexion of thumbs to the forearm	0	1	2
Hyperextension of the elbows beyond 10°	0	1	2
Hyperextension of the knees beyond 10°	0	1	2
Forward flexion of the trunk with knees fully extended and palms resting on the floor	0	1	

A total score of ≥5 is considered positive for the presence of generalized joint hypermobility.

Since laxity decreases with age, individuals with a Beighton score of <5 may be considered positive based on historical observations. The five-point questionnaire is as follows (adapted from Hakim & Grahame [2003]):

1. Can you now (or could you ever) place your hands flat on the floor without bending your knees?
2. Can you now (or could you ever) bend your thumb to touch your forearm?
3. As a child, did you amuse your friends by contorting your body into strange shapes or could you do the splits?
4. As a child or teenager, did your shoulder or kneecap dislocate on more than one occasion?
5. Do you consider yourself "double-jointed"?

Note: A "yes" answer to ≥2 questions suggests joint hypermobility with 80%-85% sensitivity and 80%-90% specificity.

Minor criteria

- Easy bruising
- Soft, doughy skin
- Skin fragility (or traumatic splitting)
- Molluscoid pseudotumors: fleshy, heaped-up lesions associated with scars over pressure points such as the elbows and knees
- Subcutaneous spheroids: small, spherical hard bodies, frequently mobile, palpable on the forearms and shins. Spheroids may be calcified and detectable radiologically.
- Hernia (or history thereof)
- Epicanthal folds
- Complications of joint hypermobility (e.g., sprains, dislocations/subluxations, pain, flexible flat foot)
- Family history of a first-degree relative with a diagnosis of cEDS

Establishing the Diagnosis

The diagnosis of cEDS **is established** in a proband with suggestive findings and a heterozygous pathogenic (or likely pathogenic) variant in one of the genes listed in Table 2 identified by molecular genetic testing.

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 variant" in this *GeneReview* is understood to include any likely pathogenic variant. (2) Identification of a heterozygous variant of uncertain significance in one of the genes listed in Table 2 does not establish or rule out the diagnosis.

Molecular genetic testing approaches can include a combination of **multigene targeted testing** and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires that

Figure 1. Skin hyperextensibility

the clinician determine which gene(s) are likely involved (see Option 1), whereas comprehensive genomic testing does not (see Option 2).

Option 1

Multigene targeted testing. Sequence analysis of *COL5A1* and *COL5A2* (multigene targeted panels may also include *COL1A1* and other EDS-related genes; see Differential Diagnosis) is performed first to detect missense, nonsense, and splice site variants and small intragenic deletions/insertions. If the multigene panel only includes *COL5A1* and *COL5A2*, targeted testing of *COL1A1* pathogenic variant c.934C>T should be done next if no *COL5A1* or *COL5A2* pathogenic variants are identified. Note: Depending on the sequencing method used, single-exon, multiexon, or whole-gene deletions/duplications may not be detected. If no variant is detected by the sequencing method used, the next step is to perform gene-targeted deletion/duplication analysis of *COL5A1* and *COL5A2* to detect exon and whole-gene deletions or duplications.

Note: (1) Multigene targeted analysis implies that the coding regions for the genes, included in the multigene panel, are enriched. (2) 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. (3) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (4) In some laboratories, panel options may include

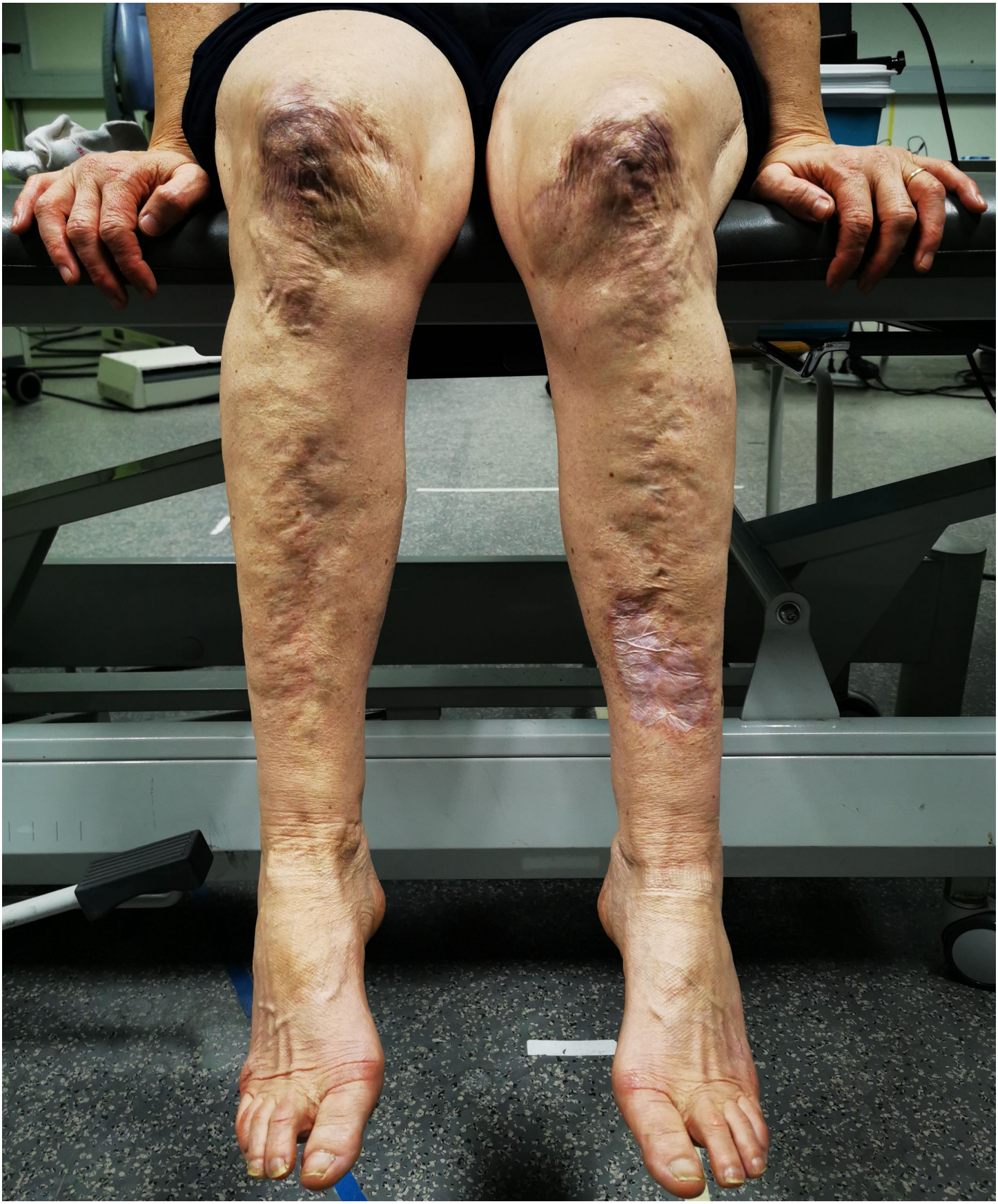

Figure 2. Widened atrophic scars

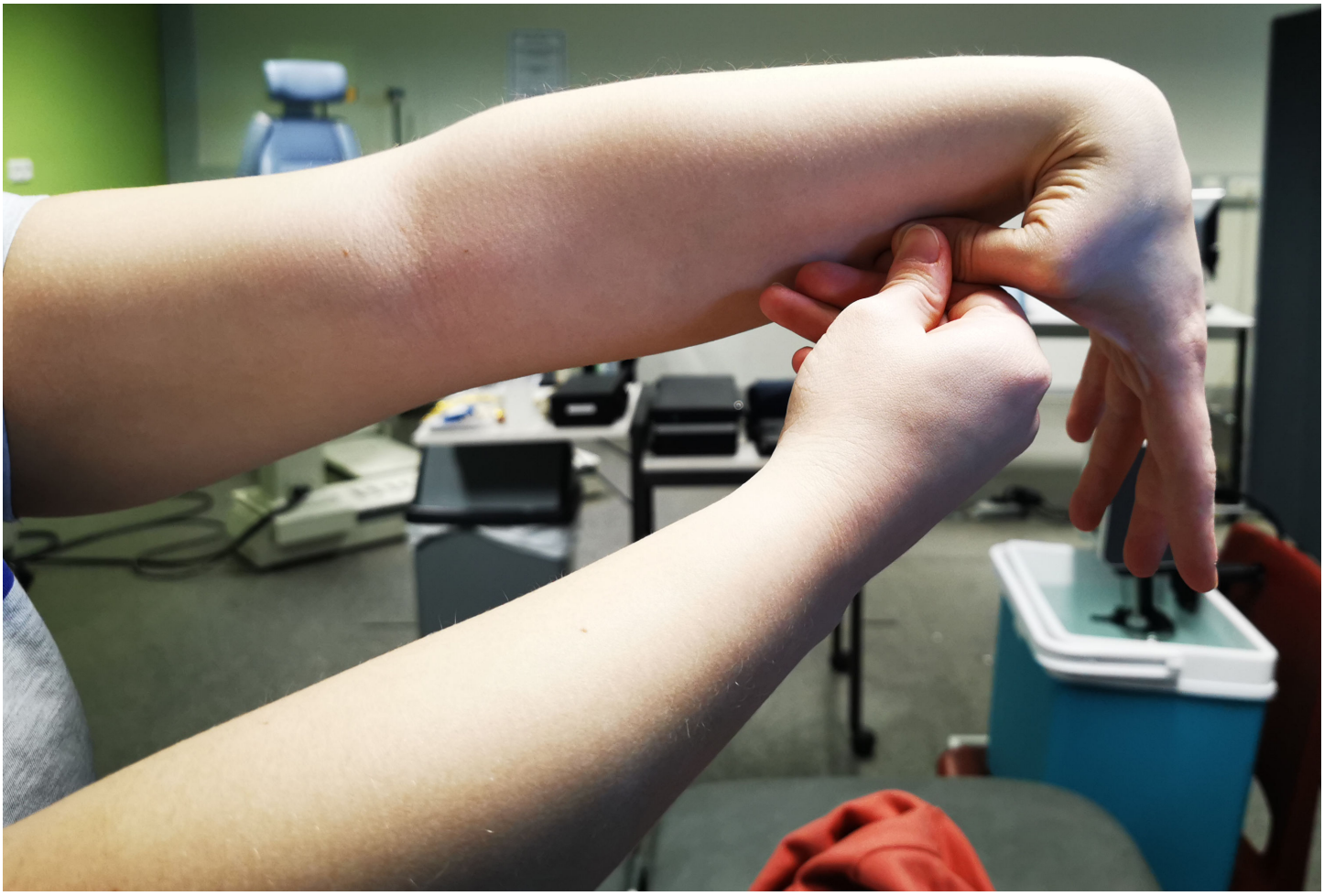

Figure 3. Flexion of the thumb to forearm, illustrating joint hypermobility

a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (5) 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 disorders characterized by hypermobility, **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 in some diagnostic centers.

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

Table 2. Molecular Genetic Testing Used in Classic Ehlers-Danlos Syndrome

Gene [1, 2]	Proportion of cEDS Attributed to Pathogenic Variants in Gene	Proportion of Probands with a Pathogenic Variant [3] Detectable by Method	
		Sequence analysis [4]	Gene-targeted deletion/ duplication analysis [5]
COL1A1	3% [6]	100% [6]	None reported [6,7]
COL5A1	81% [8]	99% [8]	1% [8]
COL5A2	16% [8]	99% [8]	1% [8, 9]

cEDS = classic Ehlers-Danlos syndrome
1. Genes are listed in alphabetic order.
2. See Table A. Genes and Databases for chromosome locus and protein.
3. See Molecular Genetics for information on variants detected in this gene.
4. 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.
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. In addition, in silico prediction software, such as ExomeDepth, is available for predicting deletions/duplications in large, comprehensive datasets (e.g., from exome sequencing).
6. Brady et al [2017], Malfait et al [2017], Colman et al [2021]
7. Large deletions in *COL1A1* have not been reported in individuals with cEDS.
8. Symoens et al [2012], Ritelli et al [2013]
9. Data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

Other Testing

***COL5A1* null allele test.** If a pathogenic variant cannot be identified on molecular genetic testing, a type V collagen abnormality can sometimes be demonstrated by the *COL5A1* null allele test if the proband is heterozygous for a polymorphic marker in *COL5A1* at the genomic DNA (gDNA) level. Copy DNA is analyzed from fibroblasts to identify the presence of one or both markers; if one marker is not expressed, that allele is assumed to be nonfunctional (i.e., "null"). This type of testing is not widely available.

Transmission electron microscopy (TEM). If molecular genetic testing is not available, TEM findings of collagen flowers on skin biopsy can support the clinical diagnosis, but do not confirm it, as collagen flowers are not pathognomonic for cEDS.

Clinical Characteristics

Clinical Description

Classic Ehlers-Danlos syndrome (cEDS) is a heritable connective tissue disorder characterized by skin hyperextensibility, abnormal wound healing, and generalized joint hypermobility.

Skin. Skin is hyperextensible; it extends easily and snaps back after release (unlike lax, redundant skin, as in cutis laxa).

The skin is soft, velvety, or doughy to the touch.

The skin is fragile, as manifested by splitting of the dermis following relatively minor trauma, especially over pressure points (knees, elbows) and areas prone to trauma (shins, forehead, chin). Skin fragility may cause dehiscence of sutured incisions in skin or mucosa.

Wound healing is poor, and stretching, thinning, and pigmentation of scars is characteristic. Scars become wide, with a "cigarette-paper"-like (papyraceous) appearance, also referred to as atrophic and/or hemosiderotic scars.

Other dermatologic features in cEDS:

- Molluscoid pseudotumors
- Subcutaneous spheroids
- Piezogenic papules: small, painful, reversible herniations of underlying adipose tissue globules through the fascia into the dermis, such as on medial and lateral aspects of the feet upon standing
- Elastosis perforans serpiginosa: characterized by skin-colored to erythematous keratotic papules, some enlarging outward in serpiginous or arcuate configurations, leaving slightly atrophic centers
- Acrocyanosis: painless constriction or narrowing of the small blood vessels in the skin (affecting mainly the hands) in which the affected areas turn blue and become cold and sweaty; localized swelling may also occur
- Chilblains: cold injuries, characterized by red, swollen skin that is tender and hot to the touch and may itch; can develop in less than two hours in skin exposed to cold

Tissue fragility. Manifestations of generalized tissue extensibility and fragility can be observed in multiple organs:

- Cervical insufficiency during pregnancy
- Inguinal and umbilical hernia
- Hiatal and incisional hernia
- Recurrent rectal prolapse in early childhood

Joints. Complications of joint hypermobility including dislocations/subluxations of large and small joints (e.g., shoulder, patella, digits, hip, radius, and clavicle) may occur and usually resolve spontaneously or are easily managed by the affected individual. Many individuals with cEDS experience chronic joint and limb pain, despite normal skeletal radiographs.

Other problems related to joint hypermobility are joint instability, foot deformities such as congenital clubfoot or pes planus, and temporomandibular joint dysfunction [Bowen et al 2017].

Neurologic features. Primary muscular hypotonia may occur and may cause delayed motor development, problems with ambulation, and mild motor disturbance in children with cEDS. Fatigue and muscle cramps are relatively frequent.

Easy bruising. Easy bruising is a common finding and manifests as spontaneous ecchymoses, frequently recurring in the same areas and causing a characteristic brownish discoloration of the skin, especially in exposed areas such as shins and knees. There is a tendency toward prolonged bleeding (e.g., following brushing of the teeth) in spite of a normal coagulation status.

Cardiovascular. Structural cardiac malformations are uncommon in cEDS.

Mitral valve prolapse and (less frequently) tricuspid valve prolapse may occur. Stringent criteria should be used for the diagnosis of mitral valve prolapse. When it does occur, mitral valve prolapse tends to be of little clinical consequence [Atzinger et al 2011].

Aortic root dilatation has been reported in individuals with cEDS [Wenstrup et al 2002, McDonnell et al 2006, Atzinger et al 2011]. It appears to be more common in young individuals and rarely progresses [Bowen et al 2017].

Individuals with cEDS are at risk for spontaneous rupture of large arteries, although the prevalence of such complications is much lower than in those with vascular EDS.

Dental. Classic EDS may be associated with abnormal dentinogenesis resulting in localized root anomalies, with shortened or bulbous roots, that lead to loosening of the teeth. Calcification of the pulp is another common finding in cEDS. This is usually of little clinical significance but may complicate root canal treatment [Lepperdinger et al 2021].

Pregnancy. Pregnancy in a woman with cEDS places both the newborn and the mother at risk for complications (see Pregnancy Management). As a whole, the complications are more frequent than in the normal population, although it is difficult to quantitate the incidence of each complication in affected individuals because no good studies exist [Kang et al 2020].

- Premature rupture of the membranes and prematurity are reported to be twice as common in fetuses with cEDS born to healthy mothers, compared with fetuses without EDS born to a mother with cEDS.
- Because of hypotonia, breech presentation is more frequent if the baby is affected and may lead to dislocation of the hips or shoulder of the newborn.
- Intrauterine growth restriction may occur.
- Perineal tearing, postpartum hemorrhage, pelvic prolapse, and incontinence following delivery may occur.

Phenotype Correlations by Gene

COL5A2. Although numbers are still limited, pathogenic variants in *COL5A2* are thought to result in a phenotype at the more severe end of the cEDS spectrum [Colman et al 2021].

Genotype-Phenotype Correlations

No genotype-phenotype correlations have emerged to date.

Penetrance

Penetrance is presumably 100% in both males and females, but in some individuals the condition is very mild, and may be undiagnosed.

Nomenclature

As a result of the 1997 Villefranche conference on EDS [Beighton et al 1998], EDS type I and type II were collectively reclassified "EDS, classical type." In 2017, the International EDS Consortium proposed a revised EDS classification system in which the nomenclature for "EDS, classical type" was changed to "classical EDS" or cEDS [Malfait et al 2017].

Prevalence

The prevalence of cEDS has been estimated at 1:20,000 [Byers 2001]. However, it is likely that some individuals with milder manifestations (previously classified as EDS type II) do not come to medical attention and thus go undetected.

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with germline pathogenic variants in *COL5A2*.

Other phenotypes associated with germline pathogenic variants in *COL1A1* and *COL5A1* are summarized in Table 3.

Table 3. Allelic Disorders

Gene	Disorder
COL1A1	The majority of pathogenic variants in *COL1A1* are assoc w/osteogenesis imperfecta.
	Arthrochalasia EDS (OMIM 130060)
	EDS/OI overlap phenotypes (OMIM 619115)
	Caffey disease (infantile cortical hyperostosis)
COL5A1	Multifocal fibromuscular dysplasia (OMIM 619329)

EDS = Ehlers-Danlos syndrome; OI = osteogenesis imperfecta

Differential Diagnosis

Other forms of Ehlers-Danlos syndrome (EDS) should be considered in individuals with easy bruising, joint hypermobility, and/or chronic joint dislocation. Clinical overlap with classic EDS (cEDS) is seen with all other forms of EDS, in particular with hypermobile EDS (hEDS) and the EDS types listed in Table 4.

Hypermobile EDS is generally considered the least severe type of EDS, although significant complications, primarily musculoskeletal, can occur. Similar to cEDS, generalized joint hypermobility, mild atrophic scarring, mild skin hyperextensibility, and soft, velvety skin are seen in hEDS. Unlike cEDS, hEDS is not associated with truly papyraceous and/or hemosiderotic scars. The diagnosis of hEDS is based entirely on clinical evaluation and family history. The gene(s) in which pathogenic variants cause hEDS are unknown.

Table 4. Ehlers-Danlos Syndrome-Related Genes of Interest in the Differential Diagnosis of Classic Ehlers-Danlos Syndrome

Gene(s)	Disorder	MOI	Clinical Features of Disorder	
			Overlapping w/cEDS	Distinguishing from cEDS
ADAMTS2	Dermatosparaxis EDS (OMIM 225410)	AR	• Atrophic scarring • Easy bruising • GJH • Skin hyperextensibility • Soft, doughy skin	• Extreme skin fragility (usually > than in cEDS) • Redundant, almost lax, skin • Unusual craniofacial features • Postnatal growth restriction
AEBP1	Classic-like EDS type 2 (OMIM 618000)	AR	• Atrophic scarring • Easy bruising • GJH • Skin hyperextensibility	• Prematurely aged appearance • Thinning of hair or (partial) alopecia
COL1A1 *COL1A2*	Arthrochalasia EDS (OMIM 130060, 617821)	AD	• Atrophic scarring • Easy bruising • GJH • Skin hyperextensibility	Bilateral congenital hip dislocation
COL1A2	Cardiac valvular EDS (OMIM 225320)	AR	• Atrophic scarring • Easy bruising • (Generalized) joint hypermobility • Skin hyperextensibility	Severe progressive cardiac valvular problems
COL3A1 [1]	Vascular EDS [1]	AD	• Atrophic scarring • Easy bruising • GJH • Skin hyperextensibility • Doughy skin	• Gastrointestinal rupture • Pneumothorax • Severe hematoma formation, incl muscle hematoma

Table 4. continued from previous page.

Gene(s)	Disorder	MOI	Clinical Features of Disorder	
			Overlapping w/cEDS	Distinguishing from cEDS
FKBP14	*FKBP14*-related kyphoscoliotic EDS	AR	• Easy bruising • GJH • Skin hyperextensibility	• Congenital muscle hypotonia • Muscle atrophy • Congenital hearing impairment
PLOD1	*PLOD1*-related kyphoscoliotic EDS	AR	• Atrophic scarring • Easy bruising • GJH • Skin hyperextensibility	Congenital muscle hypotonia
TNXB	*TNXB*-related classic-like EDS	AR	• Easy bruising • GJH • Skin hyperextensibilityy • Velvety skin	Absence of atrophic scarring

AD = autosomal dominant; AR = autosomal recessive; cEDS = classic Ehlers-Danlos syndrome; EDS = Ehlers-Danlos syndrome; GJH = generalized joint hypermobility; MOI = mode of inheritance
1. Glutamic acid to lysine substitutions in *COL3A1* have been reported in individuals with features of both vascular EDS and cEDS [Ghali et al 2019].

Management

For a detailed review of complications and management of classic Ehlers-Danlos syndrome (cEDS), see Bowen et al [2017].

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with cEDS, the evaluations summarized in Table 5 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 5. Classic Ehlers-Danlos Syndrome: Recommended Evaluations Following Initial Diagnosis

System/Concern	Evaluation	Comment
Skin	Clinical exam of skin w/assessment of skin hyperextensibility, atrophic scars & bruises, & other manifestations of cEDS	
Joints	Eval of joint mobility w/Beighton score	
Neurologic	Eval for hypotonia & motor development in infants & children	
Hematologic	• Assessment for easy bruising &/or prolonged bleeding • Eval of clotting factors (platelet count, aPTT, PT, thrombin time) if severe easy bruising is present	
Cardiovascular	Echocardiogram w/aortic diameter measurement	
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families re nature, MOI, & implications of cEDS to facilitate medical & personal decision making

cEDS = classic Ehlers-Danlos syndrome; MOI = mode of inheritance; aPTT = activated partial thromboplastin time; PT = prothrombin time
1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 6).

Table 6. Classic Ehlers-Danlos Syndrome: Treatment of Manifestations

Manifestation/ Concern	Treatment	Considerations/Other
Skin	• Dermal wounds should be closed w/o tension, preferably in 2 layers. • Deep stitches should be applied generously. • Cutaneous stitches should be left in place twice as long as usual, & additional fixation of adjacent skin w/adhesive tape can help prevent stretching of the scar.	• Very young children w/pronounced skin fragility can wear protective pads or bandages over the forehead, knees, & shins to avoid skin tears. • Older children who are active can wear soccer pads or ski stockings w/shin padding during activities.
Joint instability	• Braces are useful to improve joint stability. • Orthopedist, rheumatologist, or physical therapist referral for knee or ankle braces as needed • Occupational therapist referral for ring splints (to stabilize interphalangeal joints) & wrist or wrist & thumb braces for small joint instability • A soft neck collar, if tolerated, may help w/neck pain & headaches. • Wheelchair or scooter as needed to decrease stress on lower-extremity joints • Wheelchair customizations (e.g., lightweight, motorized, seat pads, specialized wheels, wheel grasps) as needed to accommodate pelvic & upper-extremity issues • A waterbed, adjustable air mattress, or viscoelastic foam mattress (&/or pillow) may increase support for improved sleep quality & less pain.	• Those w/hypotonia, joint instability, & chronic pain may need to adapt lifestyle accordingly. • Note: Surgical stabilization of joints may lead to disappointing, or only temporary, improvement.
Joint pain – analgesics	• Acetaminophen: 4,000 mg daily in 3-4 divided doses • NSAIDs, as tolerated by upper GI symptoms, for arthralgia, myalgia, & secondary inflammatory conditions (e.g., bursitis, tendinitis, costochondritis, postdislocation pain) • COX-2 inhibitors have similar efficacy to NSAIDS but may be better tolerated. • Topical lidocaine (cream or patch) may be useful for localized pain. • Topical capsaicin is of questionable utility but is safe. • Tramadol w/acetaminophen & NSAID or COX-2 inhibitor before resorting to other opioids (Nausea is the most common side effect.) • Opioids for myofascial pain & neuropathic pain; should be reserved after failing the above medications. Administer w/other analgesics to minimize total opioid requirements. Typically used chronically (or at least several months), the primary formulation should be long acting (e.g., sustained-release oxycodone or morphine or topical fentanyl patch) w/short-acting forms of the same drug as needed for breakthrough pain. Routine use of ≥2 daily doses of a short-acting form should prompt an	• Bruising is not a contraindication to NSAID therapy, but occasionally requires dose reduction or change to a COX-2 inhibitor. • Those w/muscle hypotonia & joint instability w/chronic pain may have to adjust lifestyle & professional choices accordingly. • Emotional support & behavioral & psychological therapy may help in developing acceptance & coping skills. • Long-term chronic pain may result in the need for mental health services.

Table 6. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
	increase in the long-acting dose or another adjustment to the pain regimen.	
Pain – other pharmaceutical treatment options	**Serotonin/norepinephrine receptor inhibitors** (SNRIs) (e.g., venlafaxine, desvenlafaxine, duloxetine, milnacipran) offer combined benefit for depression & neuropathic pain.	Venlafaxine may ↑ blood pressure a few points, which may be helpful for those w/neurally mediated hypotension.
	Some **anti-seizure medications** (e.g., gabapentin, pregabalin, topiramate, lamotrigine) have been used in cEDS, are effective for neuropathic pain, & can be used in addition to tricyclic antidepressants &/or SNRIs.	• All require gradual titration before reaching therapeutic levels. • Gabapentin should be titrated as tolerated to at least 1,200 mg 3x per day before declaring failure, but dose is often limited by sedation &/or GI side effects. • Pregabalin, titrated to at least 300 mg divided 2-3x/day, tends to be better tolerated than gabapentin.
	Short courses of **steroids** can be very effective for controlling acute flares of pain assoc w/secondary inflammation.	Classic EDS is not an intrinsically inflammatory condition, & there is no role for chronic steroid use.
	Muscle relaxants in combination w/analgesics to treat myofascial spasm & neuropathic pain	• Limited by sedation; metaxalone may be least sedating • Muscle relaxants may ↑ joint instability by ↓ muscle tone.
	Magnesium (topical as Epsom salt baths or oral) may ↓ muscle spasm & pain.	• No specific formulation or dosage is established as superior. • Adverse effects (sedation, nausea, abdominal pain, & diarrhea) are more common w/oral rather than topical supplementation.
	• **Tricyclic antidepressants** are often effective for neuropathic pain, w/additional benefits of mild sedation (for those w/sleep disturbance) & a little mood elevation. • Typical doses are nortriptyline (25-150 mg) or trazadone (50-300 mg) every evening.	• Constipation, a common side effect, can be managed w/fluids, fiber, stool softeners, & laxatives. • For those w/diarrhea-predominant irritable bowel syndrome, the constipating effect may be therapeutic.
	Glucosamine & chondroitin may help to prevent or treat osteoarthritis in the general population.	These have not been studied specifically in cEDS but are not contraindicated.
	Cannabinoids such as dronabinol & marijuana (where legal) may be helpful for several different types of pain.	Benefits should be weighed against the potential for dependency &/or psychoactive effects.
	Benzodiazepines may offer some short-term reduction in muscle spasm.	Routine use of benzodiazepines is not recommended, because of the high risk of tolerance, dependency, & addiction.
Neurologic	• Physiotherapeutic program for children w/hypotonia &/or delayed motor development • Non-weight-bearing muscular exercise (e.g., swimming) to promote muscular development & coordination	

Table 6. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Hematologic	Ascorbic acid (vitamin C) may ↓ easy bruising; general dose is 2 g per day for adults, w/proportionally reduced doses for children.	
	DDAVP® (desmopressin) may be useful to normalize bleeding time.	DDAVP® may be beneficial w/bruising or epistaxis, or before procedures such as dental extractions.
Cardiovascular	Standard treatment for cardiovascular manifestations	

cEDS = classic Ehlers-Danlos syndrome; GI = gastrointestinal; NSAIDs = nonsteroidal anti-inflammatory drugs

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 7 are recommended.

Table 7. Classic Ehlers-Danlos Syndrome: Recommended Surveillance

System/Concern	Evaluation	Frequency
Skin	Assessment for skin fragility	At each visit or as needed
Joints/Pain	Assessment for joint instability, occupational & physical therapy needs, mobility issues, pain	
Neurologic	Eval for hypotonia & motor development	At each visit in infants & children
Hematologic	Assessment for easy bruising &/or prolonged bleeding	At each visit
	Eval of clotting factors (platelet count, aPTT, PT, & thrombin time)	If severe easy bruising is present
Cardiovascular	Echocardiogram	**In those w/normal initial echocardiogram:** • Children: frequency of follow up per pediatric cardiologist • Adults: no follow-up echocardiogram necessary
		In those w/abnormal echocardiogram (aortic dilatation, mitral valve prolapse): annually

aPTT = activated partial thromboplastin time; PT = prothrombin time

Agents/Circumstances to Avoid

Sports with heavy joint strain should be avoided (contact sports, fighting sports, football, running).

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger at-risk relatives of an affected individual by molecular genetic testing of the pathogenic variant in the family in order to identify as early as possible those who would benefit from prompt initiation of treatment and preventive measures.

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

Pregnancy Management

Because of the increased risk for skin lacerations, postpartum hemorrhages, and prolapse of the uterus and/or bladder, monitoring of women throughout pregnancy and in the postpartum period is recommended.

Ascorbic acid (vitamin C) may reduce easy bruising. In general, 2 g per day is recommended for adults; however, no strict guidelines exist regarding recommended dose during the third trimester of pregnancy.

Physiotherapist referral should be made to address pelvic instability and pain.

Monitoring for intrauterine growth restriction and cervical insufficiency through cervical length screening can be valuable.

Monitoring of pregnant women for preterm labor is warranted during the third trimester, when the risk for preterm premature rupture of the membranes is increased.

For vaginal delivery, prompt episiotomy should be considered to prevent excessive perineal damage.

Prophylactic desmopressin and tranexamic acid, along with postpartum oxytocin, should be considered in view of the increased risk for postpartum hemorrhage.

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

Classic Ehlers-Danlos syndrome (cEDS) is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- Approximately 50% of individuals diagnosed with cEDS have an affected parent.
- A proband with cEDS may have the disorder as the result of a *COL1A1*, *COL5A1*, or *COL5A2* pathogenic variant that occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic, apparently unaffected parent. Approximately 50% of individuals diagnosed with cEDS have the disorder as the result of a *de novo* pathogenic variant.
- If the proband appears to be the only affected family member (i.e., a simplex case), recommendations for both parents of the proband include:
    - Evaluation for manifestations of cEDS (i.e., physical examination of the skin with special attention to delayed wound healing, easy bruising, joint hypermobility or recurrent dislocations, and chronic articular pain);
    - Molecular genetic testing for the cEDS-related pathogenic variant identified in the proband to evaluate the genetic status of the parents and inform recurrence risk assessment.

- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant.
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism [Chesneau et al 2021, Micale et al 2021]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ (gonadal) cells only.
- The family history of some individuals diagnosed with cEDS may appear to be negative because of failure to recognize the disorder in family members with very mild phenotypes. Therefore, an apparently negative family history cannot be confirmed without appropriate clinical evaluation of the parents and/or molecular genetic testing (to establish that neither parent is heterozygous for the pathogenic variant identified in the proband).

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 known to have the pathogenic variant identified in the proband, the risk to the sibs is 50%. Intrafamilial phenotypic variability is observed; the severity, specific manifestations, and progression of the disorder are variable and cannot be predicted in a sib who inherits a pathogenic variant.
- If the cEDS-related pathogenic variant identified in the proband cannot be detected in the leukocyte DNA of either parent, the recurrence risk to sibs is estimated to be slightly greater than that of the general population because of the possibility of parental germline mosaicism. Paternal mosaicism for a *COL5A1* pathogenic variant has been reported in two families [Chesneau et al 2021, Micale et al 2021].
- If the parents appear to be unaffected but their genetic status is unknown, the risk to the sibs of a proband appears to be low but increased over that of the general population because of the possibility of a very mild phenotype in an undiagnosed heterozygous parent and of parental germline mosaicism.

Offspring of a proband. Each child of an individual with cEDS has a 50% chance of inheriting the 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, the parent's family members may be at risk.

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.

At-risk individuals. The severity, specific symptoms, and progression of the disorder are variable and cannot be predicted based on family history or results of molecular genetic testing.

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 or at risk.

Prenatal Testing and Preimplantation Genetic Testing

Once the cEDS-related pathogenic variant has been identified in an affected family member, prenatal and preimplantation genetic testing are possible. However, the severity, specific manifestations, and progression of

cEDS are variable and cannot be predicted based on family history or the presence of a pathogenic variant identified on prenatal testing.

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. Classic Ehlers-Danlos Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
COL1A1	17q21.33	Collagen alpha-1(I) chain	COL1A1 @ LOVD	COL1A1	COL1A1
COL5A1	9q34.3	Collagen alpha-1(V) chain	COL5A1 @ LOVD	COL5A1	COL5A1
COL5A2	2q32.2	Collagen alpha-2(V) chain	COL5A2 @ LOVD	COL5A2	COL5A2

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 Classic Ehlers-Danlos Syndrome (View All in OMIM)

120150	COLLAGEN, TYPE I, ALPHA-1; COL1A1

Table B. continued from previous page.

120190	COLLAGEN, TYPE V, ALPHA-2; COL5A2
120215	COLLAGEN, TYPE V, ALPHA-1; COL5A1
130000	EHLERS-DANLOS SYNDROME, CLASSIC TYPE, 1; EDSCL1

Molecular Pathogenesis

COL1A1 encodes the pro-α1 chains of type I collagen, whose triple helix comprises two α1 chains and one α2 chain. Type I collagen is a fibril-forming collagen found in most connective tissues and is abundant in bone, cornea, dermis, and tendon.

COL5A1 and *COL5A2* encode the pro-α1 and the pro-α2 chain of type V collagen, respectively. Type V collagen is a minor fibril-forming collagen that is mainly present as $[\alpha1(V)]_2$ α2(V) heterotrimers in skin, bone, and tendon. It forms heterotypic fibrils with type I collagen and regulates the diameter of those fibrils, presumably through its partially retained amino-terminal propeptide. The pathogenic mechanism underlying classic Ehlers-Danlos syndrome (cEDS) is hypothesized to be "functional" haploinsufficiency of type V collagen, caused either by loss of expression of one *COL5A1* allele, inefficient trafficking of mutated protein through the endoplasmic reticulum, or impaired incorporation of mutated α chains into type V collagen heterotrimers. Given its important regulatory role during the formation of heterotypic type I/V collagen fibrils, reduced availability of type V collagen is expected to negatively impact interactions with other extracellular matrix (ECM) components and hence compromises the general organization of the ECM [Symoens et al 2012].

Table 8. Classic Ehlers-Danlos Syndrome: Gene-Specific Mechanism of Disease Causation

Gene [1]	Mechanism of Disease Causation
COL1A1 c.934C>T	Unknown; possible dominant-negative activity
COL5A1	• Haploinsufficiency: diminished type V collagen caused by nonsense or frameshift variants may alter normal collagen fibrillogenesis [Symoens et al 2012, Ritelli et al 2013]. • Dominant-negative activity: the abnormal type V collagen interferes w/protein derived from the normal allele.
COL5A2	Likely dominant-negative activity; the abnormal forms interfere with protein derived from the normal allele.

1. Genes from Table 1 in alphabetic order.

***COL1A1*-specific laboratory technical considerations**. Although most pathogenic variants in *COL1A1* cause osteogenesis imperfecta, the specific missense variant c.934C>T causes cEDS.

Table 9. Pathogenic Variants Referenced in This *GeneReview* by Gene

Gene [1]	Reference Sequences	DNA Nucleotide Change	Predicted Protein Change	Comment [Reference]
COL1A1	NM_000088.4 NP_000079.2	c.934C>T	p.Arg312Cys	Pathogenic variant identified in 35 persons from 12 families [Colman et al 2022]
COL5A1	NM_000093.5 NP_000084.3	c.1588G>A	p.Gly530Ser	May be disease modifying in the heterozygous state & disease causing in the homozygous state [Giunta & Steinmann 2000, Giunta et al 2002]

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. Genes from Table 1 are in alphabetic order.

Chapter Notes

Author Notes

The Malfait Lab (Center for Medical Genetics Ghent [CMGG] at Ghent University Hospital and Department for Biomolecular Medicine at Ghent University, Belgium) performs integrative translational research on Ehlers-Danlos syndromes (EDS). CMGG at Ghent University Hospital, in which the Malfait Lab is embedded, has a strong reputation as an internationally recognized center of expertise for research, diagnostics, and clinical management related to a range of hereditary connective tissue disorders (CTD), including, among others, EDS.

At the Malfait Lab, PI Prof Fransiska Malfait, MD, PhD, and Postdoctoral Fellow Delfien Syx, PhD, lead studies in the following areas of interest:

- Unraveling the molecular basis of hereditary CTD, with a special focus on EDS and other hypermobility-related disorders, and studying their natural history and genotype-phenotype correlations;
- Elucidating molecular and physiologic mechanisms underlying hereditary CTD pathogenesis, using an integrated approach of in vitro and in vivo techniques, on tissue samples of humans and animal models (zebra fish, mice);
- Studying prevalence, nature, and pathophysiologic mechanisms of pain in individuals with EDS and in relevant animal models.

Fransiska Malfait (fransiska.malfait@ugent.be) is actively involved in clinical research regarding individuals with EDS. Prof Malfait would be happy to communicate with persons who have any questions regarding diagnosis of EDS or other considerations.

Prof Malfait is also interested in hearing from clinicians treating families affected by EDS in whom no causative variant has been identified through molecular genetic testing of the genes known to be involved in this group of disorders.

Contact Dr Sofie Symoens (sofie.symoens@ugent.be) to inquire about cEDS-related variants of uncertain significance.

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- 24 July 2008 (me) Comprehensive update posted live

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- 20 June 2003 (rw, ad) Original submission

References

Published Guidelines / Consensus Statements

Bowen JM, Sobey GJ, Burrows NP, Colombi M, Lavallee ME, Malfait F, Francomano CA. Ehlers-Danlos syndrome, classical type. Am J Med Genet C Semin Med Genet. 2017;175:27-39. [PubMed]

Malfait F, Francomano C, Byers P, Belmont J, Berglund B, Black J, Bloom L, Bowen JM, Brady AF, Burrows NP, Castori M, Cohen H, Colombi M, Demirdas S, De Backer J, De Paepe A, Fournel-Gigleux S, Frank M, Ghali N, Giunta C, Grahame R, Hakim A, Jeunemaitre X, Johnson D, Juul-Kristensen B, Kapferer-Seebacher I, Kazkaz H, Kosho T, Lavallee ME, Levy H, Mendoza-Londono R, Pepin M, Pope FM, Reinstein E, Robert L, Rohrbach M, Sanders L, Sobey GJ, Van Damme T, Vandersteen A, van Mourik C, Voermans N, Wheeldon N, Zschocke J, Tinkle B. The 2017 international classification of the Ehlers–Danlos syndromes. Am J Med Genet C Semin Med Genet. 2017;175:8-26. [PubMed]

Literature Cited

Atzinger CL, Meyer RA, Khoury PR, Gao Z, Tinkle BT. Cross-sectional and longitudinal assessment of aortic root dilation and valvular anomalies in hypermobile and classic Ehlers-Danlos syndrome. J Pediatr. 2011;158:826-30.e1. PubMed PMID: 21193204.

Beighton P, De Paepe A, Steinmann B, Tsipouras P, Wenstrup RJ. Ehlers-Danlos syndromes: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). Am J Med Genet. 1998;77:31–7. PubMed PMID: 9557891.

Brady AF, Demirdas S, Fournel-Gigleux S, Ghali N, Giunta C, Kapferer-Seebacher I, Kosho T, Mendoza-Londono R, Pope MF, Rohrbach M, Van Damme T, Vandersteen A, van Mourik C, Voermans N, Zschocke J, Malfait F. The Ehlers-Danlos syndromes, rare types. Am J Med Genet C Semin Med Genet. 2017;175:70-115. PubMed PMID: 28306225.

Bowen JM, Sobey GJ, Burrows NP, Colombi M, Lavallee ME, Malfait F, Francomano CA. Ehlers-Danlos syndrome, classical type. Am J Med Genet C Semin Med Genet. 2017;175:27-39. PubMed PMID: 28192633.

Byers PH. Disorders of collagen biosynthesis and structure. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The Metabolic and Molecular Bases of Inherited Disease*. 2 ed. Edinburgh, UK: Churchill Livingstone; 2001:1065-81.

Chesneau B, Plancke A, Rolland G, Chassaing N, Coubes C, Brischoux-Boucher E, Edouard T, Dulac Y, Aubert-Mucca M, Lavabre-Bertrand T, Plaisancié J, Khau Van Kien P. Parental mosaicism in Marfan and Ehlers-Danlos syndromes and related disorders. Eur J Hum Genet. 2021;29:771-9. PubMed PMID: 33414558.

Colman M, Castori M, Micale L, Ritelli M, Colombi M, Ghali N, Van Dijk F, Marsili L, Weeks A, Vandersteen A, Rideout A, Legrand A, Frank M, Mirault T, Ferraris A, Di Giosaffatte N, Grammatico P, Grunert J, Frank C, Symoens S, Syx D, Malfait F. Atypical variants in COL1A1 and COL3A1 associated with classical and vascular Ehlers-Danlos syndrome overlap phenotypes: expanding the clinical phenotype based on additional case reports. Clin Exp Rheumatol. 2022;40:46-62. PubMed PMID: 35587586.

Colman M, Syx D, De Wandele I, Dhooge T, Symoens S, Malfait F. Clinical and molecular characteristics of 168 probands and 65 relatives with a clinical presentation of classical Ehlers-Danlos syndrome. Hum Mutat. 2021;42:1294-306. PubMed PMID: 34265140.

Ghali N, Baker D, Brady AF, Burrows N, Cervi E, Cilliers D, Frank M, Germain DP, Hulmes DJS, Jacquemont ML, Kannu P, Lefroy H, Legrand A, Pope FM, Robertson L, Vandersteen A, von Klemperer K, Warburton R, Whiteford M, van Dijk FS. Atypical COL3A1 variants (glutamic acid to lysine) cause vascular Ehlers-Danlos syndrome with a consistent phenotype of tissue fragility and skin hyperextensibility. Genet Med. 2019;21:2081-91. PubMed PMID: 30837697.

Giunta C, Nuytinck L, Raghunath M, Hausser I, De Paepe A, Steinmann B. Homozygous Gly530Ser substitution in COL5A1 causes mild classical Ehlers-Danlos syndrome. Am J Med Genet. 2002;109:284–90. PubMed PMID: 11992482.

Giunta C, Steinmann B. Compound heterozygosity for a disease-causing G1489E [correction of G1489D] and disease-modifying G530S substitution in COL5A1 of a patient with the classical type of Ehlers-Danlos syndrome: an explanation of intrafamilial variability? Am J Med Genet. 2000;90:72–9. PubMed PMID: 10602121.

Hakim AJ, Grahame R. A simple questionnaire to detect hypermobility: an adjunct to the assessment of patients with diffuse musculoskeletal pain. Int J Clin Pract. 2003;57:163-6. PubMed PMID: 12723715.

Kang J, Hanif M, Mirza E, Jaleel S. Ehlers-Danlos syndrome in pregnancy: a review. Eur J Obstet Gynecol Reprod Biol. 2020;255:118-23. PubMed PMID: 33113401.

Lepperdinger U, Zschocke J, Kapferer-Seebacher I. Oral manifestations of Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2021;187:520-6. PubMed PMID: 34741498.

Malfait F, Francomano C, Byers P, Belmont J, Berglund B, Black J, Bloom L, Bowen JM, Brady AF, Burrows NP, Castori M, Cohen H, Colombi M, Demirdas S, De Backer J, De Paepe A, Fournel-Gigleux S, Frank M, Ghali N, Giunta C, Grahame R, Hakim A, Jeunemaitre X, Johnson D, Juul-Kristensen B, Kapferer-Seebacher I, Kazkaz H, Kosho T, Lavallee ME, Levy H, Mendoza-Londono R, Pepin M, Pope FM, Reinstein E, Robert L, Rohrbach M, Sanders L, Sobey GJ, Van Damme T, Vandersteen A, van Mourik C, Voermans N, Wheeldon N, Zschocke J, Tinkle B. The 2017 international classification of the Ehlers-Danlos syndromes. Am J Med Genet C Semin Med Genet. 2017;175:8-26. PubMed PMID: 28306229.

McDonnell NB, Gorman BL, Mandel KW, Schurman SH, Assanah-Carroll A, Mayer SA, Najjar SS, Francomano CA. Echocardiographic findings in classical and hypermobile Ehlers-Danlos syndromes. Am J Med Genet A. 2006;140:129-36. PubMed PMID: 16353246.

Micale L, Foiadelli T, Russo F, Cinque L, Bassanese F, Granatiero M, Fusco C, Savasta S, Castori M. Gonosomal mosaicism for a novel COL5A1 pathogenic variant in classic Ehlers-Danlos syndrome. Genes (Basel). 2021;12:1928. PubMed PMID: 34946877.

Remvig L, Duhn PH, Ullman S, Kobayasi T, Hansen B, Juul-Kristensen B, Jurvelin JS, Arokoski J. Skin extensibility and consistency in patients with Ehlers-Danlos syndrome and benign joint hypermobility syndrome. Scand J Rheumatol. 2009;38:227-30. PubMed PMID: 19169910.

Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24. PubMed PMID: 25741868.

Ritelli M, Dordoni C, Venturini M, Chiarelli N, Quinzani S, Traversa M, Zoppi N, Vascellaro A, Wischmeijer A, Manfredini E, Garavelli L, Calzavara-Pinton P, Colombi M. Clinical and molecular characterization of 40 patients with classic Ehlers-Danlos syndrome: identification of 18 COL5A1 and 2 COL5A2 novel mutations. Orphanet J Rare Dis. 2013;8:58. PubMed PMID: 23587214.

Stenson PD, Mort M, Ball EV, Chapman M, Evans K, Azevedo L, Hayden M, Heywood S, Millar DS, Phillips AD, Cooper DN. The Human Gene Mutation Database (HGMD®): optimizing its use in a clinical diagnostic or research setting. Hum Genet. 2020;139:1197-207. PubMed PMID: 32596782.

Symoens S, Syx D, Malfait F, Callewaert B, De Backer J, Vanakker O, Coucke P, De Paepe A. Comprehensive molecular analysis demonstrates type V collagen mutations in over 90% of patients with classic EDS and allows to refine diagnostic criteria. Hum Mutat. 2012;33:1485-93. PubMed PMID: 22696272.

Wenstrup RJ, Meyer RA, Lyle JS, Hoechstetter L, Rose PS, Levy HP, Francomano CA. Prevalence of aortic root dilation in the Ehlers-Danlos syndrome. Genet Med. 2002;4:112–7. PubMed PMID: 12180144.

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