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Ehlers-Danlos Syndrome, Classic Type

Synonym: Ehlers-Danlos Syndrome, Classical Type. Includes: Ehlers-Danlos Syndrome Type I, Ehlers-Danlos Syndrome Type II

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Summary

Disease characteristics. Ehlers-Danlos syndrome (EDS), classic type is a connective tissue disorder characterized by skin hyperextensibility, abnormal wound healing, and joint hypermobility. It includes two previously designated subtypes (EDS type I and EDS type II) that are now recognized to form a continuum of clinical findings. The skin is smooth, velvety to the touch, and hyperelastic; i.e., it extends easily and snaps back after release (unlike lax, redundant skin, as in cutis laxa). 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 delayed, and stretching of scars after apparently successful primary wound healing is characteristic. Complications of joint hypermobility, such as dislocations of the shoulder, patella, digits, hip, radius, and clavicle, usually resolve spontaneously or are easily managed by the affected individual. Other features include hypotonia with delayed motor development, fatigue and muscle cramps, and easy bruising. Less common findings include mitral and tricuspid valve prolapse, aortic root dilatation, and spontaneous rupture of large arteries.

Diagnosis/testing. The diagnosis of EDS, classic type is established by family history and clinical examination. Quantitative and qualitative studies of type V collagen chains are usually not useful in confirming a diagnosis. At least 50% of individuals with classic EDS have an identifiable mutation in *COL5A1* or *COL5A2*, the genes encoding type V collagen; however, this number may be an underestimate, since no prospective molecular studies of *COL5A1* and *COL5A2* have been performed in a clinically well-defined group.

Management. *Treatment of manifestations:* Children with hypotonia and delayed motor development benefit from physiotherapy. Non-weight-bearing exercise promotes muscle strength and coordination. Anti-inflammatory drugs may alleviate joint pain. Those with hypotonia, joint instability, and chronic pain may need to adapt lifestyles accordingly. 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. Cardiovascular problems are treated in a standard manner.

Prevention of primary manifestations: 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. Ascorbic acid (vitamin C) may reduce bruising.

Surveillance: Yearly echocardiogram when aortic dilatation and/or mitral valve prolapse are present.

Agents/circumstances to avoid: Acetylsalicylate; sports that strain joints.

Genetic counseling. EDS, classic type is inherited in an autosomal dominant manner. It is estimated that approximately 50% of affected individuals have inherited the disease-causing mutation from an affected parent, and approximately 50% of affected individuals have a *de novo* disease-causing mutation. Each child of an affected individual has a 50% chance of inheriting the mutation. Prenatal testing for pregnancies at increased risk is possible for families in which the disease-causing mutation has been identified in an affected family member.

Diagnosis

Clinical Diagnosis

The diagnosis of Ehlers-Danlos syndrome (EDS), classic type is established by family history and clinical examination. Diagnostic criteria were developed by a medical advisory group in a conference (sponsored by the Ehlers-Danlos Foundation [USA] and the Ehlers-Danlos Support Group [UK]) at Villefranche in 1997 [Beighton et al 1998; click [Guidelines](#) for full text (pdf)].

The combination of the first three **major diagnostic criteria** should have a high specificity for EDS, classic type. The presence of one or more **minor criteria** contributes to the diagnosis of EDS, classic type but is not sufficient to establish the diagnosis.

Major diagnostic criteria for the classic type of EDS

- **Skin hyperextensibility.** Skin hyperextensibility (see [Figure 1](#)) should be tested at a neutral site (one not subjected to mechanical forces or scarring), such as the volar surface of the forearm. It is measured by pulling up the skin until resistance is felt. In young children, hyperextensibility of the skin is difficult to assess because of abundant subcutaneous fat.
- **Widened atrophic scars.** (see [Figure 2](#)) (a manifestation of tissue fragility)
- **Joint hypermobility.** Joint hypermobility (see [Figure 3](#)) depends on age, gender, and family as well as ethnic backgrounds. Joint hypermobility in classic EDS is 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 semi-quantification of joint hypermobility (see [Table 1](#)).
- Positive family history

Table 1. Beighton's 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	0	1	

A total score of ≥ 5 defines hypermobility.

Minor diagnostic criteria for the classic type of EDS

- Smooth, velvety skin
- Molluscoid pseudotumors: fleshy, heaped-up lesions associated with scars over pressure points such as the elbows and knees
- Subcutaneous spheroids: small, cyst-like, hard shot-like nodules, freely moveable in the subcutis over the bony prominences of the legs and arms. They occur in approximately one third of affected individuals, are numerous, and feel like hard grains of rice. X-ray reveals an outer calcified layer with a translucent core. The spheroids represent subcutaneous fat globules that have lost their blood supply, becoming fibrosed and calcified.
- Complications of joint hypermobility (e.g., sprains, dislocations/subluxations, pes planus)
- Muscle hypotonia, delayed gross motor development
- Easy bruising
- Manifestations of tissue extensibility and fragility (e.g., hiatal hernia, anal prolapse in childhood, cervical insufficiency)
- Surgical complications (postoperative hernias)

Testing

Electron microscopy of a skin biopsy in EDS, classic type often suggests disturbed collagen fibrillogenesis. A "cauliflower" deformity of collagen fibrils is characteristic [Hausser & Anton-Lamprecht 1994]. However, these findings are not specific for EDS and thus not diagnostic. Furthermore, ultrastructural changes, usually most pronounced in the central parts of the reticular dermis, may be missed if the skin biopsy is not full thickness.

Biochemical testing on cultured dermal fibroblasts. Collagen protein analysis is performed on cultured fibroblasts, derived from a skin biopsy in order to obtain a source of protein for electrophoretic analysis of collagen types I, III, and V. The collagens are labeled and analyzed on SDS-polyacrylamide gel electrophoresis. Abnormal proteins migrate differently on the gel when compared to control samples. Since type V collagen is synthesized by fibroblasts at low levels, alterations in electrophoretic mobility are poorly reproducible, making this an ineffective method for routine diagnostic evaluation. The test, however, helps to exclude other subtypes of EDS (e.g., the vascular, kyphoscoliotic, arthrochalasis, and dermatosparaxis types) in individuals in whom clinical differential diagnosis is difficult. Rarely, an abnormal electrophoretic pattern for type I collagen is detected due to the presence of an arginine-to-cysteine substitution in *COL1A1* coding for the pro $\alpha 1$ (I) collagen chain of type I collagen [Nuytinck et al 2000, Malfait et al 2007]

Molecular Genetic Testing

Genes. In the majority of affected families ($\geq 50\%$), the disease-causing mutation is identified in the genes encoding type V collagen, *COL5A1* and *COL5A2*. However, since no prospective molecular studies of *COL5A1* and *COL5A2* have been performed in a clinically well-defined patient group, this number may underestimate the real proportion of individuals with classic EDS harboring a mutation in one of these genes.

Evidence for locus heterogeneity. A *COL1A1* mutation, p.Arg134Cys, was identified in two unrelated children with classic EDS [Nuytinck et al 2000]. The same substitution was subsequently identified in three unrelated persons with aneurysms and rupture of medium-sized arteries in young adulthood. These people also had thin and hyperextensible skin, easy bruising, and abnormal wound healing [Malfait et al 2007; Malfait and De Paepe, personal observation]. Mutations in *COL1A1* are, however, not a major cause of classic EDS [Malfait et al 2005].

Clinical testing

- **Sequence analysis.** Approximately 50% of individuals with classic EDS have an identifiable mutation in *COL5A1* or *COL5A2*. *COL5A1* null alleles are detected in approximately 30%-40% of individuals with classic EDS [Malfait et al 2005].
- **Deletion/duplication analysis.** The usefulness of such testing has not been demonstrated, as no deletions or duplications involving *COL5A1* or *COL5A2* as causative of classic EDS have been reported.
- ***COL5A1* null allele test.** The *COL5A1* null allele test determines if the individual is heterozygous for one of several *COL5A1* polymorphic exonic markers in gDNA and then establishes at the cDNA level whether both alleles are expressed. If only one of the two *COL5A1* alleles is present in cDNA, it is assumed that the absent allele is null. Since this test examines both gDNA and cDNA, *COL5A1* null allele testing requires cultured skin fibroblasts. It does not identify mutations within *COL5A1* [Malfait et al 2005].

Table 2. Summary of Molecular Genetic Testing Used in Ehlers-Danlos Syndrome, Classic Type

Gene Symbol	Proportion of EDS, Classic Type Attributed to Mutations in This Gene	Test Method	Mutations Detected
<i>COL5A1</i>	46% ¹	Sequence analysis	Sequence variants ²
		Deletion / duplication analysis ³	Exonic and whole-gene deletions / duplications ⁴
<i>COL5A2</i>	4% ¹	Sequence analysis	Sequence variants ²
		Deletion / duplication analysis ³	Exonic and whole-gene deletions / duplications ⁴

1. Malfait et al [2005], Malfait & De Paepe [2005]

2. Examples of mutations detected by sequence analysis may include small intragenic deletions/insertions and missense, nonsense, and splice site mutations.

3. Testing that identifies deletions/duplications not readily detectable by sequence analysis of the coding and flanking intronic regions of genomic DNA; included in the variety of methods that may be used are: quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and chromosomal microarray (CMA) that includes this gene/chromosome segment.

4. No deletions or duplications involving *COL5A1* or *COL5A2* have been reported to cause Ehlers-Danlos syndrome, classic type. (Note: By definition, deletion/duplication analysis identifies rearrangements that are not identifiable by sequence analysis of genomic DNA.)

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, [click here](#).

Testing Strategy

To confirm/establish the diagnosis in a proband. Molecular genetic testing for classic EDS is complicated by the large number of exons in the coding sequences (66 in *COL5A1* and 52 in *COL5A2*) and the wide distribution of mutations. When a clinical diagnosis of classic EDS is suspected, we recommend the following evaluations:

- **Perform sequence analysis** by Sanger sequencing of *COL5A1* and *COL5A2* either on gDNA or cDNA. We recommend starting with sequence analysis of *COL5A1* on gDNA, since most individuals with classic EDS harbor a unique mutation in this gene, leading to the introduction of a premature termination codon and nonsense-mediated decay of mRNA. When no *COL5A1* mutation is found, sequence analysis of *COL5A2* should be performed.
- **Perform *COL5A1* null allele test and biochemical testing.** If sequence analysis of both *COL5A1* and *COL5A2* does not identify a causal variant in a person with the phenotype of classic EDS, the authors recommend obtaining a skin biopsy in order to perform a *COL5A1* null allele test and biochemical testing.

Prenatal diagnosis and preimplantation genetic diagnosis (PGD) for at-risk pregnancies require prior identification of the disease-causing mutation in the family.

Genetically Related (Allelic) Disorders

No other phenotypes are associated with mutations in *COL5A1* or *COL5A2*.

Clinical Description

Natural History

Ehlers-Danlos syndrome (EDS) is a connective tissue disorder characterized by skin hyperextensibility, abnormal wound healing, and joint hypermobility. Previously, two subtypes, EDS type I and EDS type II, differing only in phenotypic severity, were recognized; it is now apparent that they form a continuum of clinical findings.

Skin

- Cutaneous hyperextensibility is one of the cardinal features of EDS in general and of classic EDS in particular. Skin extends easily and snaps back after release (unlike lax, redundant skin, as in cutis laxa).
- The skin is smooth and velvety 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 delayed, and stretching of scars after apparently successful primary wound healing is characteristic. Scars become wide, with a "cigarette-paper"-like or papyraceous appearance.
- Other dermatologic features in classic EDS:
 - Molluscoid pseudotumors (see [Clinical Diagnosis](#))
 - Subcutaneous spheroids (see [Clinical Diagnosis](#))
 - 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: a rare skin condition of unknown etiology characterized by skin-

colored to erythematous keratotic papules, some enlarging outwards in serpiginous or arcuate configurations, leaving slightly atrophic centers

- Acrocyanosis: a painless disorder caused by 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 a red swollen skin that is tender, 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 are 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 of the shoulder, patella, digits, hip, radius, and clavicle may occur and usually resolve spontaneously or are easily managed by the affected individual. Some individuals with classic EDS may experience chronic joint and limb pain, despite normal skeletal radiographs.
- Other problems related to the joint hypermobility are joint instability, foot deformities such as congenital clubfoot or pes planus, temporomandibular joint dysfunction, joint effusions, and osteoarthritis [[Hagberg et al 2004](#), [De Coster et al 2005a](#), [De Coster et al 2005b](#)].

Neurologic features. Primary muscular hypotonia may occur and may cause delayed motor development, problems with ambulation, and mild motor disturbance. Fatigue and muscle cramps are relatively frequent. Rarely, CSF leak has been reported to cause postural hypotension and headache in individuals with classic EDS [[Schievink et al 2004](#)].

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 classic EDS.
- Mitral valve prolapse and, less frequently, tricuspid valve prolapse may occur. Stringent criteria should be used for the diagnosis of mitral valve prolapse.
- Aortic root dilatation may be more common than previously thought [[Wenstrup et al 2002](#)]. A recent retrospective study showed that three out of 50 (6%) individuals with classic EDS had aortic dilatation at their first echocardiogram, which was performed at a median age of 16 years. However, the dilatation tended to be of little clinical consequence and the mitral valve prolapse is rarely severe. Medical or surgical intervention is rarely necessary for either [[Atzinger et al 2011](#)].
- Spontaneous rupture of large arteries, along with intracranial aneurysms and arteriovenous fistulae, may

occur in the rare individual with a severe form of classic EDS.

Pregnancy in a woman with classic EDS bears risk for the newborn as well as for the mother. As a whole, these complications are more frequent than in the normal population; however, it is difficult to quantitate the incidence of each complication in affected individuals because no good studies exist:

- Premature rupture of the membranes and prematurity can occur when the mother is affected, and also when the fetus is affected, especially in the most severe forms.
- 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.
- In affected women, tearing of the perineal skin by forceps and, after delivery, extension of episiotomy incisions and prolapse of the uterus and/or bladder may occur.

Genotype-Phenotype Correlations

The number of individuals described with mutations in *COL5A1* or *COL5A2* is relatively small. Although there can be some variability in severity of the phenotype, no genotype/phenotype correlations have emerged to date. In particular, no difference in severity is noted in individuals with a *COL5A1* null mutation as compared to individuals with a structural mutation or those in whom no mutation can be detected.

- Mutations in *COL5A1* that encode the amino-terminal region of the pro α 1(V) collagen chain appear to be associated with a phenotype that can differ slightly from the classic EDS phenotype.
- A p.Gly530Ser substitution in the amino-terminal propeptide of the α 1(V) chain may be disease-modifying when present in the heterozygous state and disease-causing in the homozygous state [[Giunta & Steinmann 2000](#), [Giunta et al 2002](#)].
- A particular splice site mutation with a complex outcome within the amino-terminal region of the pro α 1(V) collagen chain was recently shown to result in a classic EDS-like phenotype with only minor cutaneous involvement (absence of the characteristic atrophic scarring) but with severe kyphoscoliosis and retinal detachment [[Symoens et al 2011](#)].

Penetrance

Inter- and intrafamilial variability in the severity of the phenotype can be great.

In some families with a non-functional (i.e., null) *COL5A1* allele, an affected member can have a very mild classic EDS phenotype, while other family members may have a severe phenotype [[Malfait & De Paepe 2005](#)].

Anticipation

Anticipation is not observed.

Nomenclature

As a result of the 1997 Villefranche conference on EDS [[Beighton et al 1998](#)], the former EDS type I and type II are now reclassified as EDS, classic type.

Prevalence

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

thus go undetected.

Differential Diagnosis

Other forms of Ehlers-Danlos syndrome (EDS) should be considered in individuals with easy bruising, joint hypermobility, and/or chronic joint dislocation. The disorders in which clinical findings overlap with the classic type of EDS include the following:

Ehlers-Danlos syndrome, hypermobility type (EDS type III). In this form, joint hypermobility is the primary manifestation. The skin is often soft or velvety and may be mildly hyperextensible. Subluxations and dislocations are common; they may occur spontaneously or with minimal trauma and can be acutely painful. Degenerative joint disease is common. Chronic pain, distinct from that associated with acute dislocations or advanced osteoarthritis, is a serious complication of the condition and can be both physically and psychologically disabling. Easy bruising is common, but atrophic scarring is more characteristic of the classic type of EDS. Joint hypermobility is the primary clinical manifestation. Skin abnormalities, such as variable skin hyperextensibility and smooth velvety skin, are found; but the presence of atrophic scars in individuals with joint hypermobility suggests the diagnosis of classic EDS.

The diagnosis of EDS, hypermobility type is based entirely on clinical evaluation and family history. In most individuals with EDS, hypermobility type, the gene in which mutation is causative is unknown and unmapped [Malfait et al 2006a]. Haploinsufficiency of *TNXB* (the gene encoding tenascin X) and heterozygosity for missense mutations in *TNXB* have been associated with EDS, hypermobility type in a small subset of affected individuals (see **Tenascin X deficiency**) [Zweers et al 2003, Zweers et al 2005]. A single occurrence of a *COL3A1* mutation in a family thought to have EDS, hypermobility type has been reported. Inheritance is autosomal dominant.

Tenascin X deficiency. Homozygous mutations have been identified in *TNXB* in individuals with an autosomal recessive EDS phenotype characterized by mild joint hypermobility, skin hyperextensibility, and easy bruising but without atrophic scarring [Schalkwijk et al 2001, Lindor & Bristow 2005]. Heterozygotes for the same mutation, especially females, appear to have an EDS hypermobility phenotype.

Familial joint hypermobility syndrome, and other syndromes in which hypermobility is found, share hypermobility of the joints with classic EDS; but the absence of skin hyperextensibility and atrophic scarring excludes the diagnosis of classic EDS.

Ehlers-Danlos syndrome, vascular type (EDS type IV) is characterized by thin, translucent skin; easy bruising; characteristic facial appearance; and arterial, intestinal, and/or uterine fragility. Affected individuals are at risk for arterial rupture, aneurysm, and/or dissection; gastrointestinal perforation or rupture; and uterine rupture during pregnancy. One fourth of individuals with EDS, vascular type experience a significant medical problem by age 20 years and more than 80% by age 40 years. The median age of death is 48 years.

The diagnosis of EDS, vascular type is based on clinical findings and confirmed by biochemical and/or molecular genetic testing. Biochemical studies in affected individuals demonstrate abnormal electrophoretic mobility and abnormal efficiency of secretion of type III procollagen by cultured dermal fibroblasts. Molecular genetic testing is used to identify mutations in *COL3A1*. Inheritance is autosomal dominant.

Ehlers-Danlos syndrome, progeroid form is a rare autosomal recessive disorder characterized by progeroid appearance with wrinkled facies, curly and fine hair, scanty eyebrows and eyelashes, and periodontitis, in addition to typical signs of EDS. It is caused by homozygous mutations in *B4GALT7*, the gene encoding beta-1,4-galactosyltransferase 7.

Ehlers-Danlos syndrome, kyphoscoliotic form (previously known as EDS type VI) is a generalized connective tissue disorder characterized by kyphoscoliosis, joint laxity, muscle hypotonia, and, in some individuals, fragility of

the ocular globe. Intelligence is normal; life span may be normal, but affected individuals are at risk for rupture of medium-sized arteries and respiratory compromise if kyphoscoliosis is severe.

EDS, kyphoscoliotic form is caused by mutation of *PLOD1*, resulting in deficient activity of the enzyme procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1 (PLOD1: lysyl hydroxylase 1). The diagnosis of EDS, kyphoscoliotic form relies on the demonstration of an increased ratio of deoxypyridinoline to pyridinoline crosslinks in urine measured by HPLC, a highly sensitive and specific test. Assay of lysyl hydroxylase enzyme activity in skin fibroblasts and molecular genetic testing of *PLOD1* are possible. Inheritance is autosomal recessive.

Ehlers-Danlos syndrome, arthrochalasia type (previously called type VIIA & B) is distinguished by congenital bilateral hip dislocation and severe joint hypermobility. Tissue fragility (including atrophic scars) and skin hyperextensibility are usually present; severity ranges from mild to severe. It is caused by mutations in *COL1A1* or *COL1A2* leading to the deletion of exon 6 of the mRNA coding for the $\alpha 1$ chain (EDS VIIA) or the $\alpha 2$ chain (EDS VIIB) of type I collagen, respectively. Inheritance is autosomal dominant.

Ehlers-Danlos syndrome, dermatosparaxis type (previously called EDS type VIIC) is characterized by extreme skin fragility, laxity, and a sagging, redundant appearance. Other distinct features are delayed closure of the fontanelles, characteristic facies, edema of the eyelids, blue sclerae, umbilical hernia, short fingers, and short stature. The disorder is caused by deficient activity of procollagen-N-proteinase, the enzyme that excises the N-terminal propeptide in procollagen types I, II, and III [Malfait et al 2005]. Inheritance is autosomal recessive.

Ehlers-Danlos syndrome, cardiac valvular form is characterized by joint hypermobility, skin hyperextensibility, and sometimes atrophic scarring, as well as cardiac valvular defects. Total absence of the pro $\alpha 2$ (I) chains of type I collagen as a result of homozygous or compound heterozygous mutations in *COL1A2* is causative [Schwarze et al 2004, Malfait et al 2006b]. Inheritance is autosomal recessive.

Classic-like EDS with propensity for arterial rupture. One arginine-to-cysteine (Arg-to-Cys) substitution in pro $\alpha 1$ (I) chain of type I collagen (p.Arg134Cys) has been identified in a series of individuals with a condition reminiscent of classic EDS that manifests as skin hyperextensibility, easy bruising, atrophic scarring, and joint hypermobility as well as a propensity for arterial rupture in adulthood [Nuytinck et al 2000, Malfait et al 2007]. Two other pro $\alpha 1$ (I) R-to-C substitutions (p.Arg396Cys and p.Arg915Cys) were also associated with rupture of medium-sized arteries, but affected individuals did not have EDS-like skin features [Malfait et al 2007]. Furthermore, a pro $\alpha 1$ (I)-p.Arg888Cys substitution was reported in a family presenting an EDS/osteogenesis imperfecta overlap phenotype [Cabral et al 2007], and a pro $\alpha 1$ (I)-p.Arg836Cys substitution was shown to be associated with autosomal dominant Caffey disease [Gensure et al 2005].

Ehlers-Danlos syndrome and periventricular nodular heterotopia. Mutations in *FLNA* have been identified in a limited number of individuals with periventricular nodular heterotopia (a neuronal migration disorder characterized by seizures and conglomerates of neural cells around the lateral ventricles of the brain) and features of EDS [Gómez-Garre et al 2006]. See X-Linked Periventricular Heterotopia.

Ehlers-Danlos syndrome spondylocheirodyplastic form is characterized by hyperextensible thin skin, easy bruising, hypermobility of the small joints with a tendency to contractures, protuberant eyes with bluish sclerae, hands with finely wrinkled palms, atrophy of the thenar muscles, and tapering fingers. Skeletal surveys show platyspondyly with moderate short stature, osteopenia, and widened metaphyses. Mutations in *SLC39A13*, encoding the membrane-bound zinc transporter SLC39A13, are causative [Giunta et al 2008]. Inheritance is autosomal recessive.

The *RIN2*-syndrome (also known as MACS syndrome) is characterized by severe progressive scoliosis, progressive facial coarsening, gingival hypertrophy, sparse hair, and skin and joint hyperlaxity. It is caused by mutations in *RIN2*, the gene encoding the Ras and Rab interactor 2 that acts as a guanine nucleotide exchange factor (GEF) for the small

GTPase Rab5, which is involved in early endocytosis [Basel-Vanagaite et al 2009, Syx et al 2010]. Inheritance is autosomal recessive.

Ehlers-Danlos syndrome musculocontractural type is characterized by craniofacial dysmorphism, hyperextensible thin skin, atrophic scarring, easy bruising, small joint hypermobility, hands with finely wrinkled palms and tapered fingers, congenital contractures of distal joints, scoliosis, progressive muscle hypotonia, and variable gastrointestinal and genitourinary involvement. The condition is caused by mutations in *CHST14*, encoding dermatan 4 sulfotransferase-1, which is involved in the biosynthesis of dermatan sulfate. Inheritance is autosomal recessive [Malfait et al 2010, Miyake et al 2010].

Classic EDS shows limited overlap with other connective tissue disorders, including variants of the following; these disorders are differentiated by other distinctive clinical features:

- **Marfan syndrome**, caused by mutation of *FBNI*, has a broad continuum of clinical manifestations involving the ocular, skeletal, and cardiovascular systems. Lens dislocation, seen in approximately 60%, is a hallmark feature. Myopia, retinal detachment, glaucoma, and early cataract formation are seen. Bone overgrowth leads to long extremities, pectus deformity (excavatum or carinatum), and joint laxity; scoliosis is common. Cardiovascular manifestations include dilatation of the aorta, a predisposition for aortic tear and rupture, mitral valve prolapse with or without regurgitation, tricuspid valve prolapse, and enlargement of the proximal pulmonary artery. Marfan syndrome is a clinical diagnosis based on family history and the observation of characteristic findings in multiple organ systems. Diagnostic criteria have been established. Inheritance is autosomal dominant.
- **Occipital horn syndrome (OHS)** (see *ATP7A*-Related Copper Transport Disorders) is characterized by "occipital horns," distinctive wedge-shaped calcifications at the sites of attachment of the trapezius muscle and the sternocleidomastoid muscle to the occipital bone. Occipital horns may be clinically palpable or observed on skull radiographs. Individuals with OHS also have lax skin and joints, bladder diverticula, inguinal hernias, and vascular tortuosity. There is no particular ease of bruising or fragility of the skin. Serum copper concentration and serum ceruloplasmin concentration are low. Mutation of *ATP7A* is causative. Inheritance is X-linked.
- Hyperextensible skin should also be distinguished from that observed in the cutis laxa syndromes and in De Bary syndrome, in which the redundant skin hangs in loose folds and only returns very slowly to its former position. In these syndromes, the skin is not fragile and wound healing is normal. The cutis laxa syndromes result from the loss or fragmentation of the elastic fiber network. They are variably associated with pulmonary, cardiac, arterial, and gastrointestinal abnormalities. Cutis laxa syndromes comprise autosomal dominant, autosomal recessive, and X-linked forms. The autosomal dominant form is caused by mutations in *ELN*, encoding elastin. Autosomal recessive forms of cutis laxa are associated with mutations in the genes encoding fibulin 4 and fibulin 5 (*FBLN4* and *FBLN5*), and more recently also with mutations in *ATP6V0A2* and *PYCRI*.

Note to clinicians: For a patient-specific 'simultaneous consult' related to this disorder, go to [SimulConsult®](#), an interactive diagnostic decision support software tool that provides differential diagnoses based on patient findings (registration or institutional access required).

Management

For a detailed review of complications and management, see [Wenstrup & Hoehstetter \[2004\]](#).

Evaluations Following Initial Diagnosis

To establish the extent of disease in an individual diagnosed with Ehlers-Danlos syndrome (EDS), classic type, the following evaluations are recommended:

- Clinical examination of the skin with assessment of skin hyperextensibility, atrophic scars and bruises, and other manifestations of classic EDS
- Evaluation of joint mobility with use of the Beighton score
- Evaluation for hypotonia and motor development in infants and children
- A baseline echocardiogram with aortic diameter measurement for individuals under age ten years
- Evaluation of clotting factors if severe easy bruising is present

Treatment of Manifestations

In children with hypotonia and delayed motor development, a physiotherapeutic program is important.

Non-weight-bearing muscular exercise, such as swimming, is useful to promote muscular development and coordination.

Individuals with muscle hypotonia and joint instability with chronic pain may have to adjust lifestyle and professional choices accordingly. Emotional support and behavioral and psychological therapy may help in developing acceptance and coping skills.

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.

For recommendations on treatment of joint laxity and dislocations, see [EDS, Hypermobility Type](#). (Note: Surgical stabilization of joints may lead to disappointing, or only temporary, improvement.)

Anti-inflammatory drugs may help with joint pain.

Long-term chronic pain may result in the need for mental health services.

Cardiovascular problems should be treated in a standard manner.

Prevention of Primary Manifestations

Very young children with pronounced skin fragility can wear protective pads or bandages over the forehead, knees, and shins in order to avoid skin tears. Older children who are active can wear soccer pads or ski stockings with shin padding during activities.

For recommendations on prevention of primary manifestations of joint laxity and dislocations, see [EDS, Hypermobility Type: Management, Prevention of Primary Manifestations](#).

Ascorbic acid (vitamin C) may reduce easy bruising but has no effect on the primary findings of skin hyperextensibility, atrophic scarring, and joint hypermobility. In general, a dose of two grams per day is recommended for adults, with proportionally reduced doses for children; however, there is no limitation.

Prevention of Secondary Complications

For recommendations on prevention of secondary manifestations of joint laxity and dislocations, see [EDS, Hypermobility Type: Management, Prevention of Secondary Complications](#).

Surveillance

If no abnormalities are found on echocardiogram in an adult, a follow-up echocardiogram is not necessary. (Because longitudinal data on progression of aortic dilation are not available, specific recommendations for follow-up in individuals with a normal aortic diameter are not available.)

Yearly echocardiogram is warranted if an abnormality such as aortic dilatation or mitral valve prolapse is present.

Agents/Circumstances to Avoid

The following should be avoided:

- Sports with heavy joint strain (contact sports, fighting sports, football, running)
- Acetylsalicylate (aspirin)

Evaluation of Relatives at Risk

See [Genetic Counseling](#) for issues related to testing of at-risk relatives for genetic counseling purposes

Pregnancy Management

Because of the increased risk of 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 (see [Prevention of Primary Manifestations](#)). In general, a dose of two grams per day is recommended for adults; however, no strict guidelines exist regarding recommended dose during the third trimester of pregnancy.

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

Therapies Under Investigation

Search [ClinicalTrials.gov](#) for access to information on clinical studies for a wide range of diseases and conditions.

Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, 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. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Ehlers-Danlos syndrome (EDS), classic type is inherited in an autosomal dominant manner.

Risk to Family Members

Parents of a proband

- It is estimated that approximately 50% of affected individuals have inherited the disease-causing mutation from an affected parent and approximately 50% of affected individuals have a *de novo* disease-causing mutation.

- The parents of a proband with an apparent *de novo* mutation should be evaluated by physical examination of the skin with special attention to delayed wound healing, easy bruising, joint hypermobility or recurrent dislocations, and chronic articular pain. If a disease-causing mutation has been identified in the proband, molecular genetic testing is performed in the parents.

Note: Although approximately 50% of individuals diagnosed with classic EDS have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members.

Sibs of a proband

- The risk to sibs of the proband depends on the genetic status of the proband's parents.
- If a parent of the proband is affected, the risk to the sibs is 50%.
- When the parents are clinically unaffected, the risk to the sibs of a proband appears to be low.
- Although no instances of germline mosaicism have been reported, it remains a theoretical possibility in a minority of cases.

Offspring of a proband. Each child of an individual with classic EDS has a 50% chance of inheriting the mutation.

Other family members of a proband. The risk to other family members depends on the status of the proband's parents. If a parent is affected or has a disease-causing mutation, his/her family members are at risk.

Related Genetic Counseling Issues

Prediction of phenotype. Because of intrafamilial clinical variability, it is not possible to predict the phenotype in family members who have inherited a disease-causing mutation.

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has the disease-causing mutation or clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation; however, the frequency of parental mosaicism is unknown. Additional explanations including alternate paternity or maternity (e.g., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning

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

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

Prenatal Testing

Prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at approximately 15 to 18 weeks' gestation or chorionic villus sampling (CVS) at approximately ten to 12 weeks' gestation. The disease-causing allele must be identified before prenatal testing can be performed.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual

period or by ultrasound measurements.

Requests for prenatal testing for conditions which (like classic EDS) do not affect intellect or life span are not common. Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing, particularly if the testing is being considered for the purpose of pregnancy termination rather than early diagnosis. Although most centers would consider decisions about prenatal testing to be the choice of the parents, discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be an option for some families in which the disease-causing mutation has been identified.

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](#).

- **Association Francaise des Syndrome d'Ehlers Danlos**

34 rue Léon Joulin

Turns 37 000

France

Email: contact@afsed.com

www.afsed.com

- **Canadian Ehlers Danlos Association**

88 De Rose Avenue

Bolton Ontario L7E 1A8

Canada

Phone: 905-951-7559

Fax: 905-761-7567

Email: ceda@rogers.com

- **Ehlers-Danlos National Foundation**

1760 Old Meadow Road

Suite 500

McLean VA 22102

Phone: 703-506-2892

Email: ednfstaff@ednf.org

www.ednf.org

- **Ehlers-Danlos Support Group**

PO Box 337

Aldershot Surrey GU12 6WZ

United Kingdom

Phone: 01252 690940

Email: director@ehlers-danlos.org

www.ehlers-danlos.org

- **National Library of Medicine Genetics Home Reference**

[Ehlers-Danlos syndrome](#)

- **Medline Plus**
[Ehler-Danlos Syndrome](#)
- **National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC)**
Phone: 800-334-8571 ext 24640
Email: gentac-registry@rti.org
[GenTAC](#)

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. Ehlers-Danlos Syndrome, Classic Type: Genes and Databases

Gene Symbol	Chromosomal Locus	Protein Name	Locus Specific	HGMD
COL5A1	9q34.3	Collagen alpha-1(V) chain	Ehlers-Danlos Syndrome Variant Database (COL5A1)	COL5A1
COL5A2	2q32.2	Collagen alpha-2(V) chain	Ehlers-Danlos Syndrome Variant Database (COL5A2)	COL5A2

Data are compiled from the following standard references: gene symbol from [HGNC](#); chromosomal locus, locus name, critical region, complementation group from [OMIM](#); protein name from [UniProt](#). For a description of databases (Locus Specific, HGMD) to which links are provided, click [here](#).

Table B. OMIM Entries for Ehlers-Danlos Syndrome, Classic Type ([View All in OMIM](#))

120190	COLLAGEN, TYPE V, ALPHA-2; COL5A2
120215	COLLAGEN, TYPE V, ALPHA-1; COL5A1
130000	EHLERS-DANLOS SYNDROME, TYPE I
130010	EHLERS-DANLOS SYNDROME, TYPE II

COL5A1

Normal allelic variants. The *COL5A1* cDNA comprises 66 exons distributed over more than 150 kb of genomic DNA.

Pathologic allelic variants. Several types of mutations have been identified in both *COL5A1* and *COL5A2*:

- The most common types of molecular defect lead to haploinsufficiency for *COL5A1* mRNA. In approximately 40% of individuals with classic EDS, nonsense or frameshift mutations are responsible for a non-functional *COL5A1* allele [[Schwarze et al 2000](#), [Wenstrup et al 2000](#), [Schwarze et al 2001](#), [Malfait et al 2005](#)]. Nonsense, frameshift, or splice-site mutations that introduce a premature termination codon are usually responsible for this non-functional *COL5A1* allele. A variety of mechanisms lead to nonsense-mediated decay of the mutation-bearing mRNA or to failure of the chains to associate. The predicted

consequence is synthesis of approximately half the amount of normal type V collagen.

- Structural mutations in *COL5A1*, which exert a dominant-negative effect, have been demonstrated in approximately ten to 15 individuals with classic EDS. In a small proportion of individuals, a mutation affects the structural integrity of type V collagen, resulting in the production of a functionally defective type V collagen protein (dominant-negative mutation). These structural mutations are most commonly splice-site mutations that result in exon skipping [Burrows et al 1998, Malfait et al 2005] and a few point mutations that result in the substitution for glycine in the triple-helical region of the collagen molecule [Giunta & Steinmann 2000, Malfait et al 2005]. A unique point mutation in *COL5A1* that changes a highly conserved cysteine residue to a serine in the C-terminal propeptide of the $\alpha 1(V)$ collagen chain has also been identified (p.Cys1639Ser) (NM_000093.3:c.4916G>C). In contrast to other disorders characterized by mutations in the fibrillar collagen genes, remarkably few mutations resulting from the substitution of a glycine by a bulkier amino acid have been found.
- A p.Gly530Ser (NM_000093.3: c.1588G>A) substitution in the amino-terminal propeptide of the $\alpha 1(V)$ chain may be disease-modifying when present in the heterozygous state and disease-causing in the homozygous state [Giunta & Steinmann 2000, Giunta et al 2002].

Normal gene product. Collagen $\alpha 1(V)$ chain (type V collagen chains). Type V collagen is a quantitatively minor fibrillar collagen that is widely distributed in a variety of tissues. It is present mainly as $[\alpha 1(V)]_2 \alpha 2(V)$ heterotrimers in skin, bone, and tendon. It forms heterotypic fibrils with type I collagen and regulates the diameter of those fibrils, presumably through its very large amino-terminal propeptide. Recent data indicate that type V collagen controls collagen fibril assembly in several tissues [Wenstrup et al 2004].

Abnormal gene product. Missense mutations in the triple helical domain of the $\alpha 1(V)$ or $\alpha 2(V)$ chains are likely to have dominant-negative activity; i.e., the mutant forms can interfere with the utilization of the normal protein derived from the normal allele. Diminished amounts, caused by premature termination of codons in *COL5A1* or mRNA product, may alter normal collagen fibrillogenesis.

COL5A2

Normal allelic variants. The *COL5A2* cDNA comprises 51 exons distributed over 67 kb.

Pathologic allelic variants. Structural mutations in *COL5A2* have been demonstrated in few individuals with classic EDS. These structural mutations are most commonly splice-site mutations that result in exon skipping [Michalickova et al 1998, Malfait et al 2005] and one point mutation that results in a substitution for glycine in the triple helical region of the collagen molecule [Richards et al 1998].

Normal gene product. Collagen $\alpha 2(V)$ chains (type V collagen chains). Type V collagen is a quantitatively minor fibrillar collagen that is widely distributed in a variety of tissues. It is present mainly as $[\alpha 1(V)]_2 \alpha 2(V)$ heterotrimers in skin, bone, and tendon. It forms heterotypic fibrils with type I collagen and regulates the diameter of those fibrils, presumably through its very large amino-terminal propeptide.

Abnormal gene product. Missense mutations in the triple helical domain of the $\alpha 1(V)$ or $\alpha 2(V)$ chains are likely to have dominant-negative activity; that is, the mutant forms can interfere with the utilization of the normal protein derived from the normal allele.

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Chapter Notes

Revision History

- 18 August 2011 (me) Comprehensive update posted live
- 11 May 2010 (cd) Revision: changes in testing
- 24 July 2008 (me) Comprehensive update posted live
- 29 May 2007 (cd) Revision: sequence analysis of entire coding region available for COL5A1 and COL5A2 and prenatal testing available
- 10 April 2006 (me) Comprehensive update posted to live Web site
- 29 October 2003 (ca) Review posted to live Web site
- 20 June 2003 (rw, ad) Original submission

Figures



Figure 1. Skin hyperextensibility



Figure 2. Widened atrophic scars



Figure 3. Passive flexion of thumbs to the forearm: manifestation of joint hypermobility

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