Ehlers-Danlos Syndrome, Classic Type

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

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About the Authors

Summary

Disease characteristics. Classic Ehlers-Danlos syndrome (EDS) is a connective tissue disorder characterized by skin hyperextensibility, abnormal wound healing, and joint hypermobility that 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 valve prolapse 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. Approximately 50% of individuals with classic EDS have an identifiable mutation in the *COL5A1* or *COL5A2* gene, the genes encoding type V collagen. Sequence analysis is available on a clinical basis. *COL5A1*

null allele testing detects a "null" *COL5A1* allele in approximately 30% of individuals with classic EDS and is available on a clinical basis.

Management. Children with EDS classic type who have hypotonia and delayed motor development benefit from a physiotherapeutic program. Non-weight-bearing muscular exercise promotes muscular development and coordination. Individuals with muscle hypotonia and joint instability with chronic pain may need to adapt their lifestyles accordingly. Dermal wounds are closed without tension, preferably in two layers. Deep stitches are applied generously, while cutaneous stitches are left in place twice as long as usual with fixation of adjacent skin to prevent scar stretching. Anti-inflammatory drugs may alleviate joint pain. Cardiovascular problems are treated in a standard manner. Close monitoring is recommended throughout pregnancy, especially during the third trimester, and post partum. Ascorbic acid (vitamin C) may reduce bruising. 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 active times. Individuals are advised to avoid acetylsalicylate and sports with heavy joint strain. Individuals with mitral valve regurgitation require antibiotic prophylaxis for bacterial endocarditis. Follow-up echocardiogram is performed yearly when aortic dilatation or mitral valve prolapse is present.

Genetic counseling. EDS classic type is inherited in an autosomal dominant manner. It is estimated that approximately 50% of affected individuals have inherited the mutant gene from an affected parent, and about 50% of affected individuals have a new disease-causing mutation. Each child of an individual with classic EDS has a 50% chance of inheriting the mutation. Prenatal testing may be available for families in which the disease-causing mutation has been identified in an affected family member.

Diagnosis

Clinical Diagnosis

The diagnosis of 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].

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 the classic type of EDS but is not sufficient to establish the diagnosis.

Major diagnostic criteria for the classic type of EDS:

- **Skin hyperextensibilty.** Skin hyperextensibility 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** (a manifestation of tissue fragility)
- **Joint hypermobility.** Joint hypermobility depends on age, gender, and family and ethnic backgrounds. Joint hypermobility in classic EDS is general, affecting both large and small joints. It is usually noted when a child starts to walk. It should be assessed using the Beighton scale [Beighton 1988], 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 floor	0	Present=1	

A total score of at least 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 about 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

Ultrastructural studies of classic EDS by electron microscopy often suggest disturbed collagen fibrillogenesis. A "cauliflower" deformity of collagen fibrils is characteristic [Hausser & Anton-Lamprecht 1994]. However, these findings are not specific for EDS and therefore 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. The chains of type V collagen are synthesized by cultured fibroblasts. However, type V collagen is synthesized by fibroblasts at low levels, so that quantitation and evaluation of alterations in electrophoretic mobilities are poorly reproducible, making this an ineffective method for routine diagnostic evaluation. Rarely, an abnormal electrophoretic pattern for type I collagen is detected because of a non-glycine substitution in the *COL1A1* gene coding for the proα1(I) collagen chain of type I collagen [Nuytinck et al 2000].

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory by at least one US CLIA-certified laboratory or a clinical laboratory outside the US. GeneTests does not independently verify information provided by laboratories and does not warrant any aspect of a laboratory's work. Listing in GeneTests does not imply that laboratories are in compliance with accreditation, licensure, or patent laws. Clinicians must communicate directly with the laboratories to verify information. —ED.

Genes. The genes encoding type V collagen, *COL5A1* and *COL5A2*, are known to be associated with the classic form of Ehlers-Danlos syndrome.

Although a *COL1A1* gene mutation, R134C, has been identified in two unrelated individuals with classic EDS [Nuytinck et al 2000], mutations in *COL1A1* are not a major cause of classic EDS.

Other loci. In about 50% of affected families, the disease-causing mutation is in *COL5A1* or *COL5A2*; other loci are unknown.

Clinical use

- Confirmatory diagnostic testing

Clinical testing. Molecular genetic testing for classic EDS is complicated by the large number of exons in the coding sequences (66 in the *COL5A1* gene and 52 in the *COL5A2* gene) and the wide distribution of mutations. Several types of mutations have been identified in both *COL5A1* and *COL5A2*, including exon-skipping mutations, mutations that result in substitutions for glycine, mutations in the region that controls chain assembly, and mutations that result in mRNA instability ("null" mutations).

- *COL5A1* **"null"** allele **testing.** Polymorphic markers in the expressed region of the genomic DNA may be used to determine if both *COL5A1* alleles have stable transcripts. Initially, testing determines if the individual is heterozygous for one of several *COL5A1* polymorphic exonic markers in genomic DNA. Then, *COL5A1* cDNA is tested to determine if both alleles are present. If only one of the two *COL5A1* alleles is present in cDNA, it is assumed that the absent allele is "null." *COL5A1* "null" allele testing requires cultured fibroblasts, as it examines both genomic DNA and cDNA. It does not identify mutations within the *COL5A1* gene. *COL5A1* null allele testing detects a "null" *COL5A1* allele in approximately 30% of individuals with classic EDS.
- **Sequence analysis.** Approximately 50% of individuals with classic EDS have an identifiable mutation in the *COL5A1* or *COL5A2* gene.

Table 2 summarizes molecular genetic testing for this disorder.

Table 2. **Molecular Genetic Testing** Used in Ehlers-Danlos Syndrome, Classic Type			
Test Method	**Mutations Detected**	**Mutation Detection Frequency** [1]	**Test Availability**
"Null" allele testing	*COL5A1* non-functional allele	30% [2]	Clinical **Testing**
Sequence analysis	*COL5A1* and *COL5A2* mutations	~50% [3]	

1. Proportion of affected individuals with a mutation(s) as classified by gene/locus, phenotype, population group, genetic mechanism, and/or test method
2. Wenstrup et al 2000 , Schwarze et al 2000 , Malfait et al 2005
3. Based on authors' findings

Interpretation of test results. For issues to consider in interpretation of sequence analysis results, click here.

Genetically Related (Allelic) Disorders

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

Clinical Description

Natural History

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
  - 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: 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 and localized swelling may also occur
  - Chillblains: 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 observed in multiple organs:

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

Joints

- Complications of joint hypermobility, such as 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 suffer from 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, Martens et al 2005 ; De Coster, van den Berghe et al 2005].

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. CSF leak has rarely 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 the classic type of 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].
- 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 woman. 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, as no good studies exist.

- Premature rupture of the membranes (if the fetus is affected) and prematurity are common. In the severe (gravis) form of classic EDS, prematurity occurs in approximately 50% of cases; in the mild (mitis) form, prematurity does not occur more frequently than normal.
- 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 the affected woman, extension of episiotomy incisions, tearing of the perineal skin by forceps, and prolapse of the uterus and/or bladder may occur after delivery.

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 so far. In particular, no difference in severity is noted in individuals with a *COL5A1* null mutation as compared to individuals with a structural mutation or to those in whom no mutation can be detected.

Penetrance

Inter- and intrafamilial variability can be great. Individuals with a non-functional *COL5A1* allele can have very mild classic EDS, while other family members may have severe classic EDS [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 the "classic subtype" of EDS.

Prevalence

The prevalence of EDS type I has been estimated to be 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 therefore go undetected.

Differential Diagnosis

For current information on availability of genetic testing for disorders included in this section, see GeneTests Laboratory Directory. —ED.

Other forms of Ehlers-Danlos syndrome 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 causative gene is unknown and unmapped [Malfait, Hakim et al 2006]. Haploinsufficiency of *TNXB* and heterozygosity for missense mutations in *TNXB*, the gene encoding tenascin X, have been associated with EDS, hypermobility type in a small subset of affected individuals (see below) [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 [Narcisi et al 1994]. 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 with classic EDS hypermobility of the joints, but the absence of skin hyperextensibility and atrophic scarring excludes the diagnosis of classic EDS.

Ehlers-Danlos syndrome, vascular type (also known as EDS 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 the *COL3A1* gene. 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 eye lashes, and periodontitis, in addition to typical signs of EDS. It is caused by homozygous mutations in *ß4GALT7*, the gene encoding galactosyltransferase I.

Ehlers-Danlos syndrome, kyphoscoliotic type (previously known as EDS 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 deficient activity of the enzyme procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1 (PLOD1: lysyl hydroxylase 1). The diagnosis of EDS, kyphoscoliotic form relies upon 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 is also available. Molecular genetic testing of the *PLOD1* gene that encodes the enzyme lysyl hydroxylase 1 is available. Inheritance is autosomal recessive.

Ehlers-Danlos syndrome, arthrochalasia type (previously called type VII A & B) is distinguished by severe joint hypermobility at birth and congenital bilateral hip dislocation. 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 skipping of either an amino acid change or deletion of all or part of exon 6, of the mRNA coding for one of the α1 chains (EDS VIIA) or the α2 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 and skin laxity, but the skin has a sagging, redundant appearance. Other distinct features are delayed closure of the fontanels, 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, and cardiac valvular defects. Total absence of the proα2(I) chains of type I collagen as a result of homozygous or compound heterozygous mutations in the *COL1A2* gene is causative [Schwarze et al 2004 ; Malfait, Symoens et al 2006]. Inheritance is autosomal recessive.

Classic-like Ehlers-Danlos syndrome with propensity for arterial rupture is reminiscent of classic EDS, with skin hyperextensibility, easy bruising, and atrophic scarring, and with propensity for arterial rupture at adult age [Author, personal observation]. Arginine-to-cysteine mutations in *COL1A1*, the gene encoding the proα1(I) chain of type I collagen, have recently been identified in a series of adults with this disorder. Inheritance is autosomal dominant.

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

- **Marfan syndrome** has a broad continuum of clinical manifestations involving the ocular, skeletal, and cardiovascular systems. Lens dislocation, seen in about 60%,

is a hallmark feature. Myopia, retinal detachment, glaucoma, and early cataract formation are seen. Bone overgrowth leads to long extremities and 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, triscuspid valve prolapse, and enlargement of the proximal pulmonary artery. Marfan syndrome is a clinical diagnosis based upon [family history] and the observation of characteristic findings in multiple organ systems. Diagnostic criteria have been established. [Molecular genetic testing] of the *FBN1* [gene] is possible. Inheritance is [autosomal dominant].

- **Occipital horn syndrome (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. A multiplex protocol of [targeted mutation analysis], [mutation scanning], and [sequence analysis] detects [mutations] in *ATP7A* in more than 95% of [affected] individuals. Inheritance is X-linked.

- **Hyperelastic skin** should also be distinguished from that observed in the cutis laxa syndromes and De Barsy 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.

Management

For a detailed review of complications and management, see [Wenstrup & Hoechstetter et al] ([2004]).

Evaluations Following Initial Diagnosis

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

- Good clinical inspection 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 those under the age of 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.
- 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.
- Careful follow-up is recommended throughout pregnancy and post partum. Monitoring is warranted during the third trimester when the risk of premature rupture of the membranes is increased.

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. No strict recommendations exist regarding third-trimester dose. In general, 2 grams per day is recommended for adults, with proportionally reduced doses for children; however, there is no limitation.

Prevention of Secondary Complications

- Very young children with pronounced skin fragility can wear protection in the form of 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 active times.
- Individuals with mitral valve regurgitation require antibiotic prophylaxis for bacterial endocarditis, following the usual prescribed regimens.

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.)

- If an abnormality such as aortic dilatation or mitral valve prolapse is found on echocardiogram, follow-up echocardiogram should be performed once a year.

Agents/Circumstances to Avoid

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

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.

Other

Genetics clinics, staffed by genetics professionals, provide information for individuals and families regarding the natural history, treatment, mode of inheritance, and genetic risks to other family members as well as information about available consumer-oriented resources. See the GeneTests Clinic Directory.

Support groups have been established for individuals and families to provide information, support, and contact with other affected individuals. The Resources section may include disease-specific and/or umbrella support organizations.

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. To find a genetics or prenatal diagnosis clinic, see the GeneTests Clinic Directory. —ED.

Mode of Inheritance

Ehlers-Danlos syndrome, 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 mutant gene from an affected parent, and about 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.

Note: Although about 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 upon 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. The risk to other family members depends upon the status of the proband's parents. If a parent is found to be affected or to have 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, but the frequency of parental mosaicism is not yet known. Additional explanations including alternate paternity 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.

DNA banking. 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. DNA banking is particularly relevant in situations in which the sensitivity of currently available testing is less than 100%. See DNA Banking for a list of laboratories offering this service.

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 about 15-18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The disease-causing allele of 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 such as classic EDS that 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, careful discussion of these issues is appropriate.

Preimplantation genetic diagnosis (PGD) may be available for families in which the disease-causing mutation has been identified. For laboratories offering PGD, see Testing .

Molecular Genetics

Information in the Molecular Genetics tables may differ from that in the text; tables may contain more recent information. —ED.

Molecular Genetics of Ehlers-Danlos Syndrome, Classic Type		
Gene Symbol	**Chromosomal Locus**	**Protein Name**
COL5A1	9q34.2-q34.3	Collagen alpha-1(V) chain
COL5A2	2q31	Collagen alpha-2(V) chain

Data are compiled from the following standard references: Gene symbol from HUGO; chromosomal locus, locus name, critical region, complementation group from OMIM; protein name from Swiss-Prot.

OMIM Entries for Ehlers-Danlos Syndrome, Classic Type
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

Genomic Databases for Ehlers-Danlos Syndrome, Classic Type					
Gene Symbol	**Entrez Gene**	**HGMD**	**GeneCards**	**GDB**	**GenAtlas**
COL5A1	120215	COL5A1	*COL5A1*	131457	*COL5A1*
COL5A2	120190	COL5A2	*COL5A2*	119064	*COL5A2*

For a description of the genomic databases listed, click here.

COL5A1

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

Pathologic allelic variants:

- The most common types of molecular defect lead to **haploinsufficiency** for the *COL5A1* mRNA. In approximately one-third of individuals with classic EDS, nonsense or frameshift mutations are responsible for a non-functional *COL5A1* allele [Wenstrup et al 2000 , Schwarze 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 about half the amount of normal type V collagen.

- Structural mutations in the *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 [Nicholls et al 1996 , Wenstrup et al 1996 , De Paepe et al 1997 , 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 the *COL5A1* gene that changes a highly conserved cysteine residue to a serine in the C-terminal propeptide of the α1(V)

collagen chain has also been identified [De Paepe et al 1997]. In contrast to other disorders characterized by mutations in the fibrillar collagen genes, remarkably few mutations have been found that result from the substitution of a glycine by a bulkier amino acid.

- A G530S substitution located in the amino-terminal propeptide of the α1(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 α1 (V) chain (type V collagen chains). Type V collagen is a quantitatively minor fibrillar collagen that is widely distributed in a variety of tissues. In skin, bone,and tendon, it is present mainly as $[\alpha1(V)]_2$ $\alpha2(V)$ heterotrimers. 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 α1(V) or α2(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 the *COL5A1* gene 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 the *COL5A2* gene 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 the substitution for glycine in the triple helical region of the collagen molecule [Richards et al 1998].

Normal gene product: Collagen α2(V) chains (type V collagen chains). Type V collagen is a quantitatively minor fibrillar collagen that is widely distributed in a variety of tissues. In skin, bone, and tendon, it is present mainly as $[\alpha1(V)]_2$, $\alpha2(V)$ heterotrimers. 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 α1(V) or α2(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.

Resources

GeneReviews provides information about selected national organizations and resources for the benefit of the reader. GeneReviews is not responsible for information provided by other organizations. -ED.

- **Association Francaise des Syndrome d'Ehlers Danlos**
  34 rue Léon Joulin
  37000 Tours
  France
  Email: m.h.boucand@wanadoo.fr
  www.afsed.com

- **Canadian Ehlers-Danlos Association**
  28 Waterbury Street
  Bolton L7E 1X2
  Canada
  Phone: 905-951-7559
  Fax: 905-761-7567
  Email: ceda@rogers.com
  www.ehlersdanlos.ca

- **Ehlers-Danlos National Foundation**
  3200 Wilshire Blvd
  Suite 1601 South Tower
  Los Angeles CA 90010
  Phone: 800-956-2902; 213-368-3800
  Fax: 213-427-0057
  Email: staff@ednf.org
  www.ednf.org

- **Ehlers-Danlos Support Group**
  PO Box 337
  Aldershot 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

🖨 **Resources Printable Copy**

References

Published Statements and Policies Regarding Genetic Testing

No specific guidelines regarding genetic testing for this disorder have been developed.

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Revision History

- 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

- **http://www.genetests.org**. Accessed [05.08.07].
- **Citing** GeneReviews