

## Ehlers-Danlos syndrome

### Description

Ehlers-Danlos syndrome is a group of disorders that affect connective tissues supporting the skin, bones, blood vessels, and many other organs and tissues. Defects in connective tissues cause the signs and symptoms of these conditions, which range from mildly loose joints to life-threatening complications.

The various forms of Ehlers-Danlos syndrome have been classified in several different ways. Originally, 11 forms of Ehlers-Danlos syndrome were named using Roman numerals to indicate the types (type I, type II, and so on). In 1997, researchers proposed a simpler classification (the Villefranche nomenclature) that reduced the number of types to six and gave them descriptive names based on their major features. In 2017, the classification was updated to include rare forms of Ehlers-Danlos syndrome that were identified more recently. The 2017 classification describes 13 types of Ehlers-Danlos syndrome.

An unusually large range of joint movement (hypermobility) occurs in most forms of Ehlers-Danlos syndrome, and it is a hallmark feature of the hypermobile type. Infants and children with hypermobility often have weak muscle tone (hypotonia), which can delay the development of motor skills such as sitting, standing, and walking. The loose joints are unstable and prone to dislocation and chronic pain. In the arthrochalasia type of Ehlers-Danlos syndrome, infants have hypermobility and dislocations of both hips at birth.

Many people with the Ehlers-Danlos syndromes have soft, velvety skin that is highly stretchy (elastic) and fragile. Affected individuals tend to bruise easily, and some types of the condition also cause abnormal scarring. People with the classical form of Ehlers-Danlos syndrome experience wounds that split open with little bleeding and leave scars that widen over time to create characteristic "cigarette paper" scars. The dermatosparaxis type of the disorder is characterized by loose skin that sags and wrinkles, and extra (redundant) folds of skin may be present.

Bleeding problems are common in the vascular type of Ehlers-Danlos syndrome and are caused by unpredictable tearing (rupture) of blood vessels and organs. These complications can lead to easy bruising, internal bleeding, a hole in the wall of the intestine (intestinal perforation), or stroke. During pregnancy, women with vascular Ehlers-Danlos syndrome may experience rupture of the uterus. Additional forms of Ehlers-Danlos syndrome that involve rupture of the blood vessels include the

kyphoscoliotic, classical, and classical-like types.

Other types of Ehlers-Danlos syndrome have additional signs and symptoms. The cardiac-valvular type causes severe problems with the valves that control the movement of blood through the heart. People with the kyphoscoliotic type experience severe curvature of the spine that worsens over time and can interfere with breathing by restricting lung expansion. A type of Ehlers-Danlos syndrome called brittle cornea syndrome is characterized by thinness of the clear covering of the eye (the cornea) and other eye abnormalities. The spondylodysplastic type features short stature and skeletal abnormalities such as abnormally curved (bowed) limbs. Abnormalities of muscles, including hypotonia and permanently bent joints (contractures), are among the characteristic signs of the musculocontractural and myopathic forms of Ehlers-Danlos syndrome. The periodontal type causes abnormalities of the teeth and gums.

## Frequency

The combined prevalence of all types of Ehlers-Danlos syndrome appears to be at least 1 in 5,000 individuals worldwide. The hypermobile and classical forms are most common; the hypermobile type may affect as many as 1 in 5,000 to 20,000 people, while the classical type probably occurs in 1 in 20,000 to 40,000 people. Other forms of Ehlers-Danlos syndrome are rare, often with only a few cases or affected families described in the medical literature.

## Causes

Variants (also known as mutations) in at least 20 genes have been found to cause the Ehlers-Danlos syndromes. Variants in the *COL5A1* or *COL5A2* gene, or rarely in the *COL1A1* gene, can cause the classical type. Variants in the *TNXB* gene cause the classical-like type and have been reported in a very small percentage of cases of the hypermobile type (although in most people with this type, the cause is unknown). The cardiac-valvular type and some cases of the arthrochalasia type are caused by *COL1A2* gene variants; variants in the *COL1A1* gene have also been found in people with the arthrochalasia type. Most cases of the vascular type result from variants in the *COL3A1* gene, although rarely this type is caused by certain *COL1A1* gene variants. The dermatosparaxis type is caused by variants in the *ADAMTS2* gene. *PLOD1* or *FKBP14* gene variants result in the kyphoscoliotic type. Other rare forms of Ehlers-Danlos syndrome result from variants in other genes.

Some of the genes associated with the Ehlers-Danlos syndromes, including *COL1A1*, *COL1A2*, *COL3A1*, *COL5A1*, and *COL5A2*, provide instructions for making pieces of several different types of collagen. These pieces assemble to form mature collagen molecules that give structure and strength to connective tissues throughout the body. Other genes, including *ADAMTS2*, *FKBP14*, *PLOD1*, and *TNXB*, provide instructions for making proteins that process, fold, or interact with collagen. Variants in any of these genes disrupt the production or processing of collagen, preventing these molecules from being assembled properly. These changes weaken connective tissues in the skin, bones, and other parts of the body, resulting in the characteristic features of the Ehlers-Danlos syndromes.

Some genes associated with recently described types of Ehlers-Danlos syndrome have functions that appear to be unrelated to collagen. For many of these genes, it is not clear how variants lead to hypermobility, elastic skin, and other features of these conditions.

#### Learn more about the genes associated with Ehlers-Danlos syndrome

- ADAMTS2
- COL1A1
- COL1A2
- COL3A1
- COL5A1
- COL5A2
- FKBP14
- PLOD1
- TNXB

#### **Additional Information from NCBI Gene:**

- AEBP1
- B3GALT6
- B4GALT7
- C1R
- C1S
- CHST14
- COL12A1
- DSE
- PRDM5
- SLC39A13
- ZNF469

#### **Inheritance**

The inheritance pattern of the Ehlers-Danlos syndromes varies by type. The classical, vascular, arthrochalasia, and periodontal forms of the disorder, and likely the hypermobile type, have an autosomal dominant pattern of inheritance. Autosomal dominant inheritance means that one copy of the altered gene in each cell is sufficient to cause the disorder. In some cases, an affected person inherits the variant from one affected parent. Other cases result from new (de novo) gene variants and occur in people with no history of the disorder in their family.

The classical-like, cardiac-valvular, dermatosparaxis, kyphoscoliotic, spondylodysplastic, and musculocontractural types of Ehlers-Danlos syndrome, as well as brittle cornea syndrome, are inherited in an autosomal recessive pattern. In autosomal recessive inheritance, two copies of a gene in each cell are altered. Most often, the parents of an individual with an autosomal recessive disorder are carriers of one copy of the altered gene but do not show signs and symptoms of the disorder.

The myopathic type of Ehlers-Danlos syndrome can have either an autosomal dominant or autosomal recessive pattern of inheritance.

## **Other Names for This Condition**

- EDS
- Ehlers Danlos disease

## **Additional Information & Resources**

### Genetic Testing Information

- Genetic Testing Registry: Ehlers-Danlos syndrome (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0013720/>)
- Genetic Testing Registry: Ehlers-Danlos syndrome dermatosparaxis type (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C2700425/>)
- Genetic Testing Registry: Ehlers-Danlos syndrome progeroid type (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C4552003/>)
- Genetic Testing Registry: Ehlers-Danlos syndrome with progressive kyphoscoliosis, myopathy, and hearing loss (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C3281160/>)
- Genetic Testing Registry: Ehlers-Danlos syndrome, autosomal recessive, cardiac valvular form (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C4303789/>)
- Genetic Testing Registry: Ehlers-Danlos syndrome, classic type (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C4552122/>)
- Genetic Testing Registry: Ehlers-Danlos syndrome, hydroxylysine-deficient (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0268342/>)
- Genetic Testing Registry: Ehlers-Danlos syndrome, musculocontractural type (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1866294/>)
- Genetic Testing Registry: Ehlers-Danlos syndrome, musculocontractural type 2 (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C3809845/>)
- Genetic Testing Registry: Ehlers-Danlos syndrome, periodontal type, 2 (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C4310681/>)
- Genetic Testing Registry: Ehlers-Danlos syndrome, procollagen proteinase deficient (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C4551623/>)
- Genetic Testing Registry: Ehlers-Danlos syndrome, progeroid type, 2 (<https://www.n>

[cbi.nlm.nih.gov/gtr/conditions/C3809210/](https://www.ncbi.nlm.nih.gov/gtr/conditions/C3809210/))

- Genetic Testing Registry: Ehlers-Danlos syndrome, type 3 (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0268337/>)
- Genetic Testing Registry: Ehlers-Danlos syndrome, type 4 (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C0268338/>)
- Genetic Testing Registry: Ehlers-Danlos syndrome, type 7A (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C3508773/>)
- Genetic Testing Registry: Ehlers-Danlos syndrome, type 7B (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C1851801/>)
- Genetic Testing Registry: Ehlers-Danlos syndrome, type 8 (<https://www.ncbi.nlm.nih.gov/gtr/conditions/C4551499/>)

### Genetic and Rare Diseases Information Center

- Arthrochalasia Ehlers-Danlos syndrome (<https://rarediseases.info.nih.gov/diseases/2084/arthrochalasia-ehlers-danlos-syndrome>)
- Brittle cornea syndrome (<https://rarediseases.info.nih.gov/diseases/1019/brittle-cornea-syndrome>)
- Cardiac-Valvular Ehlers-Danlos syndrome (<https://rarediseases.info.nih.gov/diseases/12613/cardiac-valvular-ehlers-danlos-syndrome>)
- Classical Ehlers-Danlos syndrome (<https://rarediseases.info.nih.gov/diseases/2088/classical-ehlers-danlos-syndrome>)
- Classical-like Ehlers-Danlos syndrome (<https://rarediseases.info.nih.gov/diseases/8507/classical-like-ehlers-danlos-syndrome>)
- Dermatosparaxis Ehlers-Danlos syndrome (<https://rarediseases.info.nih.gov/diseases/2089/dermatosparaxis-ehlers-danlos-syndrome>)
- Ehlers-Danlos syndrome, dysfibronectinemic type (<https://rarediseases.info.nih.gov/diseases/8508/ehlers-danlos-syndrome-dysfibronectinemic-type>)
- Ehlers-Danlos syndromes (<https://rarediseases.info.nih.gov/diseases/6322/ehlers-danlos-syndromes>)
- Hypermobile Ehlers-Danlos syndrome (<https://rarediseases.info.nih.gov/diseases/2081/hypermobile-ehlers-danlos-syndrome>)
- Kyphoscoliotic Ehlers-Danlos syndrome (<https://rarediseases.info.nih.gov/diseases/2083/kyphoscoliotic-ehlers-danlos-syndrome>)
- Musculocontractural Ehlers-Danlos syndrome (<https://rarediseases.info.nih.gov/diseases/8486/musculocontractural-ehlers-danlos-syndrome>)
- Periodontal Ehlers-Danlos syndrome (<https://rarediseases.info.nih.gov/diseases/12474/periodontal-ehlers-danlos-syndrome>)
- Spondylodysplastic Ehlers-Danlos syndrome (<https://rarediseases.info.nih.gov/diseases/9991/spondylodysplastic-ehlers-danlos-syndrome>)
- Vascular Ehlers-Danlos syndrome (<https://rarediseases.info.nih.gov/diseases/2082/>)

vascular-ehlers-danlos-syndrome)

#### Patient Support and Advocacy Resources

- Disease InfoSearch (<https://www.diseaseinfosearch.org/>)
- National Organization for Rare Disorders (NORD) (<https://rarediseases.org/>)

#### Research Studies from ClinicalTrials.gov

- ClinicalTrials.gov (<https://clinicaltrials.gov/ct2/results?cond="Ehlers-Danlos syndrome">;) )

#### Catalog of Genes and Diseases from OMIM

- BRITTLE CORNEA SYNDROME 1 (<https://omim.org/entry/229200>)
- CARDIAC VALVULAR DYSPLASIA, X-LINKED (<https://omim.org/entry/314400>)
- EHLERS-DANLOS SYNDROME WITH PLATELET DYSFUNCTION FROM FIBRONECTIN ABNORMALITY (<https://omim.org/entry/225310>)
- EHLERS-DANLOS SYNDROME, ARTHROCHALASIA TYPE, 1 (<https://omim.org/entry/130060>)
- EHLERS-DANLOS SYNDROME, AUTOSOMAL DOMINANT, TYPE UNSPECIFIED (<https://omim.org/entry/130090>)
- EHLERS-DANLOS SYNDROME, BEASLEY-COHEN TYPE (<https://omim.org/entry/608763>)
- EHLERS-DANLOS SYNDROME, CARDIAC VALVULAR TYPE (<https://omim.org/entry/225320>)
- EHLERS-DANLOS SYNDROME, CLASSIC TYPE, 1 (<https://omim.org/entry/130000>)
- EHLERS-DANLOS SYNDROME, CLASSIC TYPE, 2 (<https://omim.org/entry/130010>)
- EHLERS-DANLOS SYNDROME, CLASSIC-LIKE (<https://omim.org/entry/606408>)
- EHLERS-DANLOS SYNDROME, CLASSIC-LIKE, 2 (<https://omim.org/entry/618000>)
- EHLERS-DANLOS SYNDROME, DERMATOSPARAXIS TYPE (<https://omim.org/entry/225410>)
- EHLERS-DANLOS SYNDROME, HYPERMOBILITY TYPE (<https://omim.org/entry/130020>)
- EHLERS-DANLOS SYNDROME, KYPHOSCOLIOTIC TYPE, 1 (<https://omim.org/entry/225400>)
- EHLERS-DANLOS SYNDROME, KYPHOSCOLIOTIC TYPE, 2 (<https://omim.org/entry/614557>)

- EHLERS-DANLOS SYNDROME, MUSCULOCONTRACTURAL TYPE, 1 (<https://omim.org/entry/601776>)
- EHLERS-DANLOS SYNDROME, MUSCULOCONTRACTURAL TYPE, 2 (<https://omim.org/entry/615539>)
- EHLERS-DANLOS SYNDROME, PERIODONTAL TYPE, 1 (<https://omim.org/entry/130080>)
- EHLERS-DANLOS SYNDROME, PERIODONTAL TYPE, 2 (<https://omim.org/entry/617174>)
- EHLERS-DANLOS SYNDROME, SPONDYLODYSPLASTIC TYPE, 1 (<https://omim.org/entry/130070>)
- EHLERS-DANLOS SYNDROME, SPONDYLODYSPLASTIC TYPE, 2 (<https://omim.org/entry/615349>)
- EHLERS-DANLOS SYNDROME, VASCULAR TYPE (<https://omim.org/entry/130050>)

#### Scientific Articles on PubMed

- PubMed (<https://pubmed.ncbi.nlm.nih.gov/?term=%28Ehlers-Danlos+Syndrome%5BMAJR%5D%29+AND+%28Ehlers-Danlos+syndrome%5BTIAB%5D%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+720+days%22%5Bdp%5D>)

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