Ehlers-Danlos syndrome

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

Previously, there were more than 10 recognized types of Ehlers-Danlos syndrome, differentiated by Roman numerals. In 1997, researchers proposed a simpler classification that reduced the number of major types to six and gave them descriptive names: the classical type (formerly types I and II), the hypermobility type (formerly type III), the vascular type (formerly type IV), the kyphoscoliosis type (formerly type VIA), the arthrochalasia type (formerly types VIIA and VIIB), and the dermatosparaxis type (formerly type VIIC). This six-type classification, known as the Villefranche nomenclature, is still commonly used. The types are distinguished by their signs and symptoms, their underlying genetic causes, and their patterns of inheritance. Since 1997, several additional forms of the condition have been described. These additional forms appear to be rare, affecting a small number of families, and most have not been well characterized.

Although all types of Ehlers-Danlos syndrome affect the joints and skin, additional features vary by type. An unusually large range of joint movement (hypermobility) occurs with most forms of Ehlers-Danlos syndrome, particularly the hypermobility type. Infants with hypermobile joints often have weak muscle tone, 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. Hypermobility and dislocations of both hips at birth are characteristic features in infants with the arthrochalasia type of Ehlers-Danlos syndrome.

Many people with Ehlers-Danlos syndrome 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 skin that sags and wrinkles. Extra (redundant) folds of skin may be present as affected children get older.

Some forms of Ehlers-Danlos syndrome, notably the vascular type and to a lesser extent the kyphoscoliosis and classical types, can involve serious and potentially life-threatening complications due to unpredictable tearing (rupture) of blood vessels. This rupture can cause internal bleeding, stroke, and shock. The vascular type of Ehlers-Danlos syndrome is also associated with an increased risk of organ rupture, including

tearing of the intestine and rupture of the uterus (womb) during pregnancy. People with the kyphoscoliosis form of Ehlers-Danlos syndrome experience severe, progressive curvature of the spine that can interfere with breathing.

Frequency

Although it is difficult to estimate the overall frequency of Ehlers-Danlos syndrome, the combined prevalence of all types of this condition may be about 1 in 5,000 individuals worldwide. The hypermobility and classical forms are most common; the hypermobility type may affect as many as 1 in 10,000 to 15,000 people, while the classical type probably occurs in 1 in 20,000 to 40,000 people.

Other forms of Ehlers-Danlos syndrome are very rare. About 30 cases of the arthrochalasia type and about 60 cases of the kyphoscoliosis type have been reported worldwide. About a dozen infants and children with the dermatosparaxis type have been described. The vascular type is also rare; estimates vary widely, but the condition may affect about 1 in 250,000 people.

Genetic Changes

Mutations in more than a dozen genes have been found to cause Ehlers-Danlos syndrome. The classical type results most often from mutations in either the *COL5A1* gene or the *COL5A2* gene. Mutations in the *TNXB* gene have been found in a very small percentage of cases of the hypermobility type (although in most cases, the cause of this type is unknown). The vascular type results from mutations in the *COL3A1* gene. *PLOD1* gene mutations cause the kyphoscoliosis type. Mutations in the *COL1A1* gene or the *COL1A2* gene result in the arthrochalasia type. The dermatosparaxis type is caused by mutations in the *ADAMTS2* gene. The other, less well-characterized forms of Ehlers-Danlos syndrome result from mutations in other genes, some of which have not been identified.

Some of the genes associated with Ehlers-Danlos syndrome, 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*, *PLOD1*, and *TNXB*, provide instructions for making proteins that process or interact with collagen. Mutations that cause the different forms of Ehlers-Danlos syndrome disrupt the production or processing of collagen, preventing these molecules from being assembled properly. These defects weaken connective tissues in the skin, bones, and other parts of the body, resulting in the characteristic features of this condition.

Inheritance Pattern

The inheritance pattern of Ehlers-Danlos syndrome varies by type. The arthrochalasia, classical, hypermobility, and vascular forms of the disorder 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 mutation from one affected parent. Other cases result from new (sporadic) gene mutations and occur in people with no history of the disorder in their family.

The dermatosparaxis and kyphoscoliosis types of Ehlers-Danlos syndrome, as well as some of the rare, less well-characterized types of the disorder, are inherited in an autosomal recessive pattern. In autosomal recessive inheritance, two copies of the 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.

Other Names for This Condition

- EDS
- Ehlers Danlos disease

Diagnosis & Management

Genetic Testing

- Genetic Testing Registry: Ehlers-Danlos syndrome
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C0013720/
- Genetic Testing Registry: Ehlers-Danlos syndrome Beasley Cohen type
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1837462/
- Genetic Testing Registry: Ehlers-Danlos syndrome dysfibronectinemic type
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1857038/
- Genetic Testing Registry: Ehlers-Danlos syndrome progeroid type
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C1869122/
- 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/C1857034/
- Genetic Testing Registry: Ehlers-Danlos syndrome, classic type
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C0268335/
- Genetic Testing Registry: Ehlers-Danlos syndrome, familial joint laxity type
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C0268349/
- 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, procollagen proteinase deficient https://www.ncbi.nlm.nih.gov/gtr/conditions/C0268345/
- Genetic Testing Registry: Ehlers-Danlos syndrome, progeroid type, 2 https://www.ncbi.nlm.nih.gov/gtr/conditions/C3809210/
- Genetic Testing Registry: Ehlers-Danlos syndrome, type 2 atypical https://www.ncbi.nlm.nih.gov/gtr/conditions/CN071419/
- 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 4 variant https://www.ncbi.nlm.nih.gov/gtr/conditions/CN071423/
- Genetic Testing Registry: Ehlers-Danlos syndrome, type 5 https://www.ncbi.nlm.nih.gov/gtr/conditions/C0268341/
- Genetic Testing Registry: Ehlers-Danlos syndrome, type 7A https://www.ncbi.nlm.nih.gov/gtr/conditions/CN071434/
- 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/C0268347/
- Genetic Testing Registry: Ehlers-Danlos syndrome, type vii, autosomal recessive https://www.ncbi.nlm.nih.gov/gtr/conditions/C2700425/
- Genetic Testing Registry: Ehlers-Danlos syndrome, unspecified autosomal dominant https://www.ncbi.nlm.nih.gov/gtr/conditions/C0220679/

<u>Other Diagnosis and Management Resources</u>

- GeneReview: Ehlers-Danlos Syndrome, Classic Type https://www.ncbi.nlm.nih.gov/books/NBK1244
- GeneReview: Ehlers-Danlos Syndrome, Hypermobility Type https://www.ncbi.nlm.nih.gov/books/NBK1279

- GeneReview: Ehlers-Danlos Syndrome, Kyphoscoliotic Form
  https://www.ncbi.nlm.nih.gov/books/NBK1462
- GeneReview: Vascular Ehlers-Danlos Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK1494
- MedlinePlus Encyclopedia: Ehlers-Danlos Syndrome
  https://medlineplus.gov/ency/article/001468.htm

General Information from MedlinePlus

- Diagnostic Tests
  https://medlineplus.gov/diagnostictests.html
- Drug Therapy
  https://medlineplus.gov/drugtherapy.html
- Genetic Counseling
  https://medlineplus.gov/geneticcounseling.html
- Palliative Care
  https://medlineplus.gov/palliativecare.html
- Surgery and Rehabilitation
  https://medlineplus.gov/surgeryandrehabilitation.html

Additional Information & Resources

MedlinePlus

- Encyclopedia: Ehlers-Danlos Syndrome
  https://medlineplus.gov/ency/article/001468.htm
- Encyclopedia: Hyperelastic Skin
  https://medlineplus.gov/ency/article/003280.htm
- Encyclopedia: Hypermobile Joints
  https://medlineplus.gov/ency/article/003295.htm
- Health Topic: Ehlers-Danlos Syndrome
  https://medlineplus.gov/ehlersdanlossyndrome.html

Genetic and Rare Diseases Information Center

- Arthrochalasia Ehlers-Danlos syndrome
  https://rarediseases.info.nih.gov/diseases/2084/arthrochalasia-ehlers-danlos-syndrome
- Classical Ehlers-Danlos syndrome
  https://rarediseases.info.nih.gov/diseases/2088/classical-ehlers-danlos-syndrome

- Dermatosparaxis Ehlers-Danlos syndrome
  https://rarediseases.info.nih.gov/diseases/2089/dermatosparaxis-ehlers-danlos-syndrome
- 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
- 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

Additional NIH Resources

- National Institute of Arthritis and Musculoskeletal and Skin Diseases: Questions and Answers About Heritable Disorders of Connective Tissue
  https://www.niams.nih.gov/Health_Info/Connective_Tissue/

Educational Resources

- Disease InfoSearch: Ehlers-Danlos syndrome
  http://www.diseaseinfosearch.org/Ehlers-Danlos+syndrome/2481
- MalaCards: ehlers-danlos syndrome
  http://www.malacards.org/card/ehlers_danlos_syndrome
- Merck Manual Consumer Version
  http://www.merckmanuals.com/home/children-s-health-issues/hereditary-connective-tissue-disorders/ehlers-danlos-syndrome
- My46 Trait Profile: Ehlers-Danlos Syndrome - Vascular Type
  https://www.my46.org/trait-document?trait=Ehlers-Danlos%20syndrome%20-%20Vascular%20type&type=profile
- Orphanet: Ehlers-Danlos syndrome due to tenascin-X deficiency
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=230839
- Orphanet: Ehlers-Danlos syndrome type 11
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=2295

- Orphanet: Ehlers-Danlos syndrome with periventricular heterotopia
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=82004
- Orphanet: Ehlers-Danlos syndrome, arthrochalasis type
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=1899
- Orphanet: Ehlers-Danlos syndrome, cardiac valvular type
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=230851
- Orphanet: Ehlers-Danlos syndrome, classic type
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=287
- Orphanet: Ehlers-Danlos syndrome, dermatosparaxis type
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=1901
- Orphanet: Ehlers-Danlos syndrome, fibronectinemic type
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=75501
- Orphanet: Ehlers-Danlos syndrome, hypermobility type
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=285
- Orphanet: Ehlers-Danlos syndrome, kyphoscoliotic and deafness type
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=300179
- Orphanet: Ehlers-Danlos syndrome, kyphoscoliotic type
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=1900
- Orphanet: Ehlers-Danlos syndrome, musculocontractural type
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=2953
- Orphanet: Ehlers-Danlos syndrome, periodontitis type
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=75392
- Orphanet: Ehlers-Danlos syndrome, progeroid type
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=75496
- Orphanet: Ehlers-Danlos syndrome, spondylocheirodysplastic type
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=157965
- Orphanet: Ehlers-Danlos syndrome, vascular-like type
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=230845
- Orphanet: Ehlers-Danlos syndrome, vascular type
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=286
- Orphanet: X-linked Ehlers-Danlos syndrome
  http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=75497

Patient Support and Advocacy Resources

- Ehlers-Danlos National Foundation
  https://ehlers-danlos.com/
- Ehlers-Danlos Support Group (UK)
  https://www.ehlers-danlos.org/
- National Organization for Rare Disorders (NORD)
  https://rarediseases.org/rare-diseases/ehlers-danlos-syndrome/
- RareConnect
  https://www.rareconnect.org/en/community/ehlers-danlos-syndrome
- Resource List from the University of Kansas Medical Center
  http://www.kumc.edu/gec/support/ehlers.html
- The Hypermobility Syndromes Association (UK)
  http://hypermobility.org/

GeneReviews

- Ehlers-Danlos Syndrome, Classic Type
  https://www.ncbi.nlm.nih.gov/books/NBK1244
- Ehlers-Danlos Syndrome, Hypermobility Type
  https://www.ncbi.nlm.nih.gov/books/NBK1279
- Ehlers-Danlos Syndrome, Kyphoscoliotic Form
  https://www.ncbi.nlm.nih.gov/books/NBK1462
- Vascular Ehlers-Danlos Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK1494

ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22ehlers-danlos+syndrome%22

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?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

OMIM

- EHLERS-DANLOS SYNDROME DUE TO TENASCIN-X DEFICIENCY
  http://omim.org/entry/606408
- EHLERS-DANLOS SYNDROME WITH PLATELET DYSFUNCTION FROM FIBRONECTIN ABNORMALITY
  http://omim.org/entry/225310
- EHLERS-DANLOS SYNDROME WITH PROGRESSIVE KYPHOSCOLIOSIS, MYOPATHY, AND HEARING LOSS
  http://omim.org/entry/614557
- EHLERS-DANLOS SYNDROME WITH SHORT STATURE AND LIMB ANOMALIES
  http://omim.org/entry/130070
- EHLERS-DANLOS SYNDROME, AUTOSOMAL DOMINANT, TYPE UNSPECIFIED
  http://omim.org/entry/130090
- EHLERS-DANLOS SYNDROME, AUTOSOMAL RECESSIVE, CARDIAC VALVULAR FORM
  http://omim.org/entry/225320
- EHLERS-DANLOS SYNDROME, BEASLEY-COHEN TYPE
  http://omim.org/entry/608763
- EHLERS-DANLOS SYNDROME, CLASSIC TYPE
  http://omim.org/entry/130000
- EHLERS-DANLOS SYNDROME, HYPERMOBILITY TYPE
  http://omim.org/entry/130020
- EHLERS-DANLOS SYNDROME, MUSCULOCONTRACTURAL TYPE, 1
  http://omim.org/entry/601776
- EHLERS-DANLOS SYNDROME, MUSCULOCONTRACTURAL TYPE, 2
  http://omim.org/entry/615539
- EHLERS-DANLOS SYNDROME, PERIODONTAL TYPE, 1
  http://omim.org/entry/130080
- EHLERS-DANLOS SYNDROME, PROGEROID TYPE, 2
  http://omim.org/entry/615349
- EHLERS-DANLOS SYNDROME, TYPE IV, AUTOSOMAL DOMINANT
  http://omim.org/entry/130050
- EHLERS-DANLOS SYNDROME, TYPE V
  http://omim.org/entry/305200

- EHLERS-DANLOS SYNDROME, TYPE VI
  http://omim.org/entry/225400
- EHLERS-DANLOS SYNDROME, TYPE VII, AUTOSOMAL DOMINANT
  http://omim.org/entry/130060
- EHLERS-DANLOS SYNDROME, TYPE VII, AUTOSOMAL RECESSIVE
  http://omim.org/entry/225410

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  Citation on PubMed: https://www.ncbi.nlm.nih.gov/pubmed/22353005
- GeneReview: Ehlers-Danlos Syndrome, Classic Type
  https://www.ncbi.nlm.nih.gov/books/NBK1244
- GeneReview: Ehlers-Danlos Syndrome, Hypermobility Type
  https://www.ncbi.nlm.nih.gov/books/NBK1279
- GeneReview: Ehlers-Danlos Syndrome, Kyphoscoliotic Form
  https://www.ncbi.nlm.nih.gov/books/NBK1462
- GeneReview: Vascular Ehlers-Danlos Syndrome
  https://www.ncbi.nlm.nih.gov/books/NBK1494
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