

Ehlers-Danlos Syndrome, Hypermobility Type

[EDS Type III, Ehlers-Danlos Syndrome Type III. Includes: Benign Hypermobility Syndrome, Familial Hypermobility Syndrome, Articular Hypermobility Syndrome]

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Summary

Disease characteristics. Ehlers-Danlos syndrome (EDS), hypermobility type is generally considered the least severe type of EDS, although significant complications, primarily musculoskeletal, can and do occur. 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.

Diagnosis/testing. 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. Haploinsufficiency of tenascin X (encoded by the gene *TNXB*) has been associated with EDS, hypermobility type in a small subset of affected individuals.

Management. *Treatment of manifestations:* physical therapy tailored to the individual; assistive devices (braces to improve joint stability; wheelchair or scooter to offload stress on lower-extremity joints; suitable mattress to improve sleep quality); pain medication tailored to symptoms; appropriate therapy for gastritis/reflux /delayed gastric emptying/irritable bowel syndrome; possible beta-blockade for progressive aortic enlargement; psychological and/or pain-oriented counseling. *Prevention of primary manifestations:* low-resistance exercise to increase muscle tone for improved joint stability; appropriate writing utensils to reduce finger and hand strain. *Prevention of secondary complications:* calcium, vitamin D, low-impact weight-bearing exercise to maximize bone density. *Surveillance:* DEXA every other year if bone loss is confirmed. *Agents/circumstances to avoid:* joint hyperextension; resistance/isometric exercise can exacerbate joint instability and pain; high-impact activity increases the risk of acute subluxation/dislocation, chronic pain, and osteoarthritis; cautious use of crutches, canes, and walkers, which put increased stress on the upper extremities.

Genetic counseling. EDS, hypermobility type is inherited in an autosomal dominant manner. Most individuals diagnosed with the syndrome have an affected parent. The proportion of cases caused by *de novo* mutations is unknown. Each child of an individual with EDS, hypermobility type has a 50% chance of inheriting the disorder. Prenatal testing is not available.

Diagnosis

Clinical Diagnosis

Clinical diagnostic criteria and a revised nomenclature for all forms of Ehlers-Danlos syndrome (EDS) were proposed by Beighton et al (1998). EDS, hypermobility type is characterized chiefly by joint laxity with soft skin and easy bruising, but other organ systems (especially gastrointestinal and cardiovascular) are frequently involved. It is distinguished from EDS, classic type by the more significant skin and soft tissue manifestations in the latter.

The diagnosis of EDS, hypermobility type is based entirely on clinical evaluation and family history. The criteria listed below reflect those proposed by Beighton et al (1998) as modified by the author's experience.

Major diagnostic criteria should all be met to establish a diagnosis of EDS, hypermobility type:

- **Joint hypermobility**, which is often confirmed by a score of five or more on the nine-point Beighton scale [Beighton et al 1973], although some individuals with objective joint laxity score fewer than five points (see The sensitivity and specificity of examination for joint hypermobility). One point is scored for each of the following:
 - Passive dorsiflexion of each fifth finger greater than 90°
 - Passive apposition of each thumb to the flexor surface of the forearm
 - Hyperextension of each elbow greater than 10°
 - Hyperextension of each knee greater than 10°
 - Ability to place the palms on the floor with the knees fully extended
- **Soft skin with normal or only slightly increased extensibility.** Skin hyperextensibility is assessed at a site lacking excess or loose skin and without evidence of prior trauma by gently pulling until resistance is met. Extensor surfaces of joints should not be used because of the presence of excess skin. An ideal location is the volar surface of the forearm, where the upper limit of normal is approximately 1-1.5 cm.
- **Absence of fragility or other significant skin or soft tissue abnormalities**, which are suggestive of other types of EDS. Such findings could include:
 - Spontaneous or easily induced skin cuts or tears
 - Spontaneous or easily induced tears or ruptures of tendons, ligaments, vessels, or other internal organs
 - Surgical complications, such as vessel rupture or sutures tearing through tissues and failing to hold
 - Spontaneous wound dehiscence
 - Recurrent or incision hernias
 - Significant skin hyperextensibility (>1.5 cm on the volar surface of the forearm)
 - Thin, translucent skin
 - Atrophic ("cigarette paper") scars (although mildly atrophic scars are sometimes seen in EDS, hypermobility type, especially in areas subject to physical stress, such as extensor surfaces and the abdominal wall)

— Molluscoid pseudotumors

Minor diagnostic criteria are supportive of but not sufficient to establish a diagnosis of EDS, hypermobility type:

- Positive family history of EDS, hypermobility type (or family history of joint laxity), without significant skin or soft tissue fragility, in a pattern consistent with autosomal dominant inheritance
- Recurrent joint dislocations or subluxations
- Chronic joint, limb, and/or back pain
- Easy bruising
- Functional bowel disorders (functional gastritis, irritable bowel syndrome)
- Neurally mediated hypotension or postural orthostatic tachycardia
- High, narrow palate
- Dental crowding

The sensitivity and specificity of examination for joint hypermobility is dependent in part on the individual's age, gender, and medical history.

- Young children (approximately age five years or younger) tend to be very flexible and are therefore difficult to assess.
- Women are, on average, more flexible than men.
- Older individuals tend to lose flexibility, and post-surgical or arthritic joints often have reduced range of motion. A history of former joint laxity or clinical demonstration of substantial laxity in multiple joints is sometimes accepted in lieu of a positive Beighton score in such cases, if the family history and other minor criteria are strongly suggestive.

Testing

The biochemical etiology of EDS, hypermobility type is unknown in most cases.

Molecular Genetic Testing

GeneReviews designates a molecular genetic test as clinically available only if the test is listed in the GeneTests Laboratory Directory by either a US CLIA-licensed laboratory or a non-US clinical laboratory. GeneTests does not verify laboratory-submitted information or warrant any aspect of a laboratory's licensure or performance. Clinicians must communicate directly with the laboratories to verify information.—ED.

Molecular Genetic Testing—Genes. Haploinsufficiency of tenascin X, encoded by the gene *TNXB*, has been associated with EDS, hypermobility type in a small subset of individuals. Haploinsufficiency of tenascin X appears to confer typical joint manifestations and soft skin, without skin hyperextensibility or hematologic manifestations [Zweers et al 2003].

- A phenotype similar to EDS, hypermobility type has been described in some but not all heterozygous relatives of individuals with an autosomal recessive form of EDS associated with tenascin X deficiency [Zweers et al 2003].
- Among another cohort of 80 individuals with hypermobility type EDS without family history of autosomal recessive tenascin X-deficient EDS, biochemical deficiency of tenascin X was found in six (7.5%), with confirmation of a mutation in the *TNXB*

gene in two (2.5%). All six of these individuals had typical joint laxity and many had soft skin, but all lacked easy bruising or mildly hyperextensible skin.

Other loci. The etiology and genetic locus (or loci) are unknown in the vast majority of cases.

Research testing. Serum tenascin X protein testing is available on a research basis only.

Genetically Related (Allelic) Disorders

No other phenotypes are associated with mutations in *TNXB*.

Clinical Description

Natural History

Ehlers-Danlos syndrome (EDS), hypermobility type is generally considered the least severe type of EDS, although significant complications, primarily musculoskeletal, do occur. Clinical variability is substantial. Most individuals who seek medical care are female. Pain and major joint complications are much less common among affected males. There is no apparent parent-of-origin effect with respect to severity.

Skin. The skin is often soft or velvety and may be mildly hyperextensible.

Piezogenic papules (small herniations of subcutaneous fat through the underlying dermis of the heel occurring only with weight bearing) are common but rarely painful.

Subcutaneous spheroids and molluscoid pseudotumors are not features of this type.

Clinically significant skin morbidity does not occur.

Musculoskeletal

- **Joint laxity.** Subluxations and dislocations are common and represent the major manifestation of the condition. They may occur spontaneously or with minimal trauma and can be acutely painful. Reduction often occurs spontaneously or can be accomplished by the patient or a friend/family member. For most patients, medical intervention for an acute dislocation is not usually necessary, but pain can last for hours or days after an event. Instability and excessive joint motion is evident on routine activity, even in the absence of overt subluxation. All sites can be involved, including the extremities, vertebral column, costo-vertebral and costo-sternal joints, clavicular articulations, and temporomandibular joints. Younger individuals and females tend to have more substantial laxity than older individuals and males.
- **Osteoarthritis.** Degenerative joint disease occurs at a younger age than in the general population, possibly because of chronic joint instability resulting in increased mechanical stress.
- **Osteoporosis.** Bone mineral density in individuals with EDS, hypermobility and classic types may be reduced by up to 0.9 standard deviation compared to healthy controls, even in young adulthood [Dolan et al 1998].

Pain. 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 psychosocially disabling [Sacheti et al 1997]. It is variable in age of onset (as early as adolescence or as late as the fifth or sixth decade), number of sites, duration, quality, severity, and response to therapy. The severity is typically greater than expected based on physical and radiologic examination, and fatigue and sleep disturbance are frequently associated. Affected individuals are often diagnosed with chronic fatigue syndrome, fibromyalgia, depression,

hypochondriasis, and/or malingering prior to recognition of joint laxity and establishment of the correct underlying diagnosis. At least two recognizable pain syndromes are likely:

- **Pain or myofascial pain**, localized around or between joints, often described as aching, throbbing, or stiff in quality, may be attributable to myofascial spasm, and palpable spasm with tender points (consistent with fibromyalgia) is often demonstrable, especially in the paravertebral musculature. Myofascial release often provides temporary relief.
- **Neuropathic pain**, variably described as electrical, burning, shooting, numb, tingling, or hot or cold discomfort, may occur in a radicular or peripheral nerve distribution or may appear to localize to an area surrounding one or more joints. Nerve conduction studies are usually non-diagnostic. Skin biopsy may reveal reduction or absence of small nerve fibers.

One hypothesis is that painful myofascial spasm occurs in response to chronic joint instability, with neuropathic pain resulting from direct nerve impingement (e.g., by subluxed vertebrae, herniated discs, vertebral osteoarthritis, or peripheral joint subluxations), and/or from mild-to-moderate nerve compression within spasmed connective tissues.

Headaches, especially migraine, are common, caused at least in part by cervical muscle tension and temporomandibular dysfunction.

Hematologic. Easy bruising is quite common, frequently without obvious cause. Mildly prolonged bleeding, epistaxis, and menometrorrhagia may also occur. Clinically, this mimics von Willebrand disease, but von Willebrand factor, platelet number and function, and coagulation factor studies are almost always normal. It is, however, possible for von Willebrand disease, idiopathic thrombocytopenia purpura, or other hemorrhagic conditions to be present independent of EDS.

Gastrointestinal. Functional bowel disorders are common and underrecognized, affecting up to 50% of individuals with EDS, hypermobility and classic types [Levy et al 1999].

Gastroesophageal reflux and gastritis may be symptomatic despite maximal doses of proton pump inhibitors with additional H2-blockers and acid-neutralizing medications.

Early satiety and delayed gastric emptying may occur and may be exacerbated by opioid (and other) medications.

Irritable bowel syndrome may manifest with diarrhea and/or constipation, associated with abdominal cramping and rectal mucus.

Cardiovascular

- **Autonomic dysfunction.** Approximately one-third to one-half of individuals with EDS, hypermobility (and classic) type report atypical chest pain, palpitations at rest or on exertion, and/or orthostatic intolerance. Holter monitoring usually shows normal sinus rhythm, but sometimes reveals premature atrial complexes or paroxysmal supraventricular tachycardia. Tilt table testing may reveal neurally mediated hypotension (NMH) and/or postural orthostatic tachycardia syndrome (POTS) [Rowe et al 1999].
- **Aortic root dilatation**, usually of a mild degree, occurs in one-quarter to one-third of individuals with EDS, classic and hypermobility types [Wenstrup et al 2002]. The severity appears to be much less than occurs in Marfan syndrome, and there is no increased risk of aortic dissection in the absence of significant dilatation. The long-

term stability or progression and ultimate prognosis are not yet known [Leier et al 1980, McDonnell et al 2006].

- **Mitral valve prolapse (MVP)** was previously considered a manifestation of all types of EDS, but this has **not** been confirmed in rigorous evaluations using modern diagnostic criteria for MVP [Dolan et al 1997]. It is possible that mild MVP not meeting diagnostic criteria (and therefore not requiring special monitoring or treatment) may also explain some of the atypical chest pain and palpitations.

Oral/dental. High, narrow palate and dental crowding are nonspecific features of most heritable disorders of connective tissue. Bifid uvula, submucous cleft palate, and overt cleft palate are not manifestations of EDS, hypermobility type, and should prompt consideration of alternative diagnoses (see Differential Diagnosis).

Periodontal disease (friability, gingivitis, gum recession) occurs in some individuals with EDS [Letourneau et al 2001, De Coster et al 2005] and is no longer considered a unique subtype of EDS [Beighton et al 1998]. The frequency of periodontal manifestations in the hypermobility type is undetermined. De Felice et al (2004) reported an abnormally complex oral microvascular network in 12 individuals with classic or hypermobility type EDS; potential correlation of this with periodontal disease has not been reported.

Temporomandibular dysfunction ("TMJ syndrome") is relatively common [De Coster et al 2005], and can be thought of as a specific example of joint degeneration and osteoarthritis.

Obstetric/gynecologic. Pregnancy may be complicated by premature rupture of membranes or rapid labor and delivery (less than four hours), but this is less likely than in the classic type. Joint laxity and pain typically increase throughout gestation, especially in the third trimester, as normally occurs during pregnancy in unaffected women. No other complications are associated with pregnancy.

Pelvic prolapse and dyspareunia occur at increased frequency in at least the classic and hypermobility types of EDS [Mcintosh et al 1995, Carley & Schaffer 2000].

Psychiatric. Depression is a common complication among all individuals with chronic pain, including those with EDS. No data are available on mood or personality disorders independent of pain among individuals with EDS.

Fragility of soft tissues with spontaneous ruptures or tears of internal organs is, by definition, not a feature of EDS, hypermobility type. Such manifestations should prompt consideration of other hereditary connective tissue disorders (see Differential Diagnosis).

Genotype-Phenotype Correlations

The genetic etiology for most cases is unknown. The few described individuals with EDS, hypermobility type resulting from haploinsufficiency of tenascin X lacked easy bruisability and mildly hyperextensible skin [Zweers et al 2003].

Penetrance

Penetrance is believed to be 100%, although expressivity is extremely variable, and careful examination may be required to demonstrate typical features, especially in older men who have never experienced a major joint complication or significant pain.

Anticipation

Anticipation is not believed to occur.

Nomenclature

The 1997 Villefranche conference [Beighton et al 1998] simplified the classification and nomenclature of the Ehlers Danlos syndromes. The former EDS type III was renamed the hypermobility type.

There is disagreement as to whether the "benign familial articular hypermobility syndrome" is identical to EDS, hypermobility type or represents a unique condition [Grahame 1999]. The distinction is subtle and relates to degree of joint complications and presence or absence of skin manifestations. However, first-degree relatives of probands with hypermobility type EDS often have relatively asymptomatic joint laxity and mild or absent skin manifestations. Therefore, the benign hypermobility syndrome is included as EDS, hypermobility type for this review.

Prevalence

The prevalence of EDS, hypermobility type is unknown. Estimates have ranged between 1:5,000 and 1:20,000, and depend in part on whether or not the familial articular hypermobility syndrome is included. Given the clinical variability and low probability of affected males being ascertained, the prevalence is likely much higher than estimated. EDS, hypermobility type may be the most common heritable disorder of connective tissue.

Differential Diagnosis

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

All types of Ehlers-Danlos syndrome (EDS) share some degree of joint laxity and skin/soft tissue manifestations.

The other forms of EDS are distinguished by additional connective tissue manifestations [Beighton et al 1998].

- **EDS, classic type** includes skin and soft tissue fragility. Mild presentations of the classic type may be mistaken for the hypermobility type. The diagnosis is sometimes revised from hypermobility to classic when the individual or a family member later develops more significant skin and soft tissue manifestations. 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 of these genes is available on a research basis only. *COL5A1* null allele testing is diagnostic in approximately 30% of individuals with classic EDS and is available on a clinical basis.
- In **EDS, vascular type**, the joint laxity is predominantly in small joints, and spontaneous rupture of hollow organs occurs. Dysfunction and/or deficiency of type III collagen, caused by mutations in the *COL3A1* gene, is responsible for all cases of EDS, vascular type. The diagnosis of EDS, vascular type is based on clinical findings and confirmed by biochemical (protein-based) and/or molecular genetic testing, which are available on a clinical basis.
- **EDS, kyphoscoliotic and dermatosparaxis types** are autosomal recessive, rare, and distinguished by more severe skin manifestations and other features. 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 on a research basis.

- **EDS, arthrochalasia type** is autosomal dominant, rare, and distinguished by congenital hip dislocation and more severe skin manifestations.

Joint laxity is a nonspecific manifestation of dozens of other disorders and syndromes. Some of these are traditionally thought of as heritable disorders of connective tissue or skeletal dysplasias, but many fall outside those general classifications. Most are easily distinguished from EDS by characteristic features and/or involvement of systems other than the joints and skin, but mild presentations can sometimes be misdiagnosed as EDS, hypermobility type. Some examples, in order of likelihood and importance, include the following:

- **Marfan syndrome** results in additional skeletal, ocular, cardiovascular, pulmonary, and skin/integument manifestations beyond those seen in EDS. Specific clinical criteria are available to establish a diagnosis of Marfan syndrome. This can be confirmed by clinically available demonstration of mutation in the *FBNI* gene. Joint hypermobility is common in the **MASS phenotype** (myopia, mitral valve prolapse, mild aortic root dilatation, striae and minor skeletal manifestations of Marfan syndrome), also caused by mutations in *FBNI*. Sometimes individuals with hypermobility EDS can have a Marfanoid build and as such resemble individuals with Marfan syndrome or a Marfan-related disorder. However, application of the clinical diagnostic criteria for Marfan syndrome and *FBNI* molecular analysis allow differentiation of these conditions.
- **Loeys-Dietz syndrome** is characterized by multiple arterial aneurysms and tortuosity. Other clinical features are variable, but may include ocular hypertelorism and bifid uvula. The presentation often mimics Marfan syndrome or EDS, vascular type, but prior to detection of the arterial abnormalities, individuals may be misdiagnosed with classic or hypermobility type EDS. The diagnosis is established by detection of a mutation in the *TGFBR1* or *TGFBR2* gene, which is clinically available.
- **Stickler syndrome**. Distinguishing features include sensorineural hearing loss, vitreoretinal abnormalities, and cleft palate. Mutations affecting one of three genes (*COL2A1*, *COL11A1*, and *COL11A2*) have been associated with Stickler syndrome. However, a few families with features of Stickler syndrome are not linked to any of these three loci, so mutations in other genes may also cause the disorder. Stickler syndrome is diagnosed based on clinical features. In many affected individuals and families the diagnosis can be confirmed by clinically available molecular genetic testing, but these results are primarily used to obtain information for genetic counseling.
- **Williams syndrome (WS)** is a contiguous gene deletion syndrome characterized by cardiovascular disease (elastin arteriopathy, peripheral pulmonary stenosis, supravalvular aortic stenosis, hypertension), distinctive facies, connective tissue abnormalities, mental retardation (usually mild), a specific cognitive profile, unique personality characteristics, growth abnormalities, and endocrine abnormalities (hypercalcemia, hypercalciuria, hypothyroidism, and early puberty). The mainstay for diagnosis is detection of the contiguous gene deletion of the Williams-Beuren syndrome critical region (WBSCR) that encompasses the elastin (*ELN*) gene. Over 99% of individuals with the clinical diagnosis of WS have this contiguous gene deletion, which can be detected using fluorescent in situ hybridization (FISH) or targeted mutation analysis. Supravalvular aortic stenosis (SVAS) is caused by mutation of the *ELN* gene (rather than deletion). Individuals with either deletion or mutation of the *ELN* gene have joint laxity, but the classic elastin arteriopathy is not seen in any type of EDS.

- **Aarskog-Scott syndrome (faciogenital dysplasia)** is an X-linked condition resulting from mutation of the *FGDI* gene. The most significant distinguishing feature is shawl scrotum, which may become less obvious in adulthood. Widow's peak, short upturned nose, other dysmorphic features and the inheritance pattern can be additional diagnostic clues. Mental retardation, which is not associated with any of the types of EDS, is sometimes present.
- **Fragile X syndrome** is not typically confused with EDS, hypermobility type. When a full mutation of the *FMRI* gene is present, fragile X syndrome is characterized by moderate mental retardation in affected males and mild mental retardation in affected females. Males may have a characteristic appearance (large head, long face, prominent forehead and chin, protruding ears), joint laxity and large testes (postpubertally). However, premutation carriers may have joint laxity and EDS-like skin findings without other major manifestations. Family history of mental retardation is helpful when present. The frequency of fragile X premutation among individuals diagnosed clinically with EDS, hypermobility type has not been studied, but fragile X syndrome has not been reported among offspring of women with EDS, hypermobility type.
- **Achondroplasia and hypochondroplasia** are distinguished by short stature with characteristic skeletal features (marked in achondroplasia, milder in hypochondroplasia). Achondroplasia can be diagnosed by characteristic clinical and radiographic findings in most affected individuals. Molecular genetic testing reveals a mutation in the *FGFR3* gene in 99% of individuals with achondroplasia and about 70% of individuals with hypochondroplasia. However, it is clear that locus heterogeneity exists for hypochondroplasia because mutations in other as-yet-unidentified genes can result in similar, if not identical, phenotypes.
- **Osteogenesis imperfecta (OI)**. Distinguished by the presence of fractures and, in some cases, dentinogenesis imperfecta (grey or brown teeth). Biochemical testing (i.e., analysis of the structure and quantity of type I collagen synthesized in vitro by cultured dermal fibroblasts) detects abnormalities in 98% of individuals with OI type II, about 90% with OI type I, about 84% with OI type IV, and about 84% with OI type III. About 90% of individuals with OI types I, II, III, and IV (but none with OI types V, VI and VII) have an identifiable mutation in either *COL1A1* or *COL1A2*.
- **Aneuploidies**, such as **Down**, **Turner**, or **Klinefelter syndrome** are usually easily recognized based on dysmorphic features and/or mental retardation. Small duplications or deletions may be less clinically obvious, but could be suggested by reduced fertility or recurrent pregnancy loss.

Chronic pain and fatigue are major features of fibromyalgia. A subset of individuals with fibromyalgia and/or chronic fatigue syndrome may have EDS as the underlying etiology.

Management

Evaluations Following Initial Diagnosis

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

- Thorough history and physical examination, especially for musculoskeletal, skin, cardiovascular, gastrointestinal, and oral/dental manifestations
- Assessment of prior experience with pharmacologic, mechanical, and/or surgical treatment of pain and joint instability, as well as current degree of pain and disability

- Baseline echocardiogram to evaluate aortic root diameter, as adjusted for age and body surface area [Roman et al 1989]. Significant aortic enlargement and/or other cardiac abnormalities should prompt consideration of alternative diagnoses.
- Tilt-table testing for individuals with orthostatic intolerance and/or tachycardia to help establish a diagnosis of postural orthostatic tachycardia and/or neurally mediated hypotension and to guide therapy
- If irritable bowel syndrome is suspected, consideration of formal gastroenterology consultation and possible colonoscopy to rule out other treatable diagnoses. Celiac disease and other causes of malabsorption are not associated with EDS, but may be coexisting diagnoses.
- Dual-energy x-ray absorptiometry (DEXA) if height loss greater than one inch is documented or x-rays are suggestive of osteopenia. Women should have their first study no later than menopause. It is unclear if or at what age men without height loss or abnormal x-rays should have a screening DEXA.
- If a history of severe or prolonged bleeding is present, consider hematologic evaluation for von Willebrand disease or other bleeding diathesis. While results are usually negative, such conditions may co-exist with hypermobility type EDS.

Treatment of Manifestations

Physical therapy

- Myofascial release (any physical therapy modality that reduces spasm) provides short-term relief of pain, lasting hours to days. While the duration of benefit is short and it must be repeated frequently, this pain relief is critical to facilitate participation in toning exercise for stabilization of the joints. Modalities must be tailored to the individual; a partial list includes heat, cold, massage, ultrasound, electrical stimulation, acupuncture, acupressure, biofeedback, and conscious relaxation.
- Transvaginal pelvic physical therapy and myofascial release (in which massage or ultrasound is applied to the pelvic musculature via a transvaginal approach) may improve dyspareunia, abdominal pain, back pain, and sometimes radicular lower-extremity pain.

Assistive devices

- Braces are useful to improve joint stability. Orthopedists, rheumatologists, and physical therapists can assist in recommending appropriate devices for commonly problematic joints such as knees and ankles. Shoulders and hips present more of a challenge for external bracing. Occupational therapists should be consulted for ring splints (to stabilize interphalangeal joints) and wrist or wrist/thumb braces. A soft neck collar, if tolerated, may help with neck pain and headaches.
- A wheelchair or scooter may be necessary to offload stress on lower extremity joints. Special wheelchair customizations such as lightweight and/or motorized chairs, seat pads, and specialized wheels and wheel grasps may be necessary to accommodate pelvic and upper extremity issues. Crutches, canes, and walkers should be used cautiously as they put increased stress on the upper extremities.
- A waterbed, adjustable air mattress, or viscoelastic foam mattress (and/or pillow) may provide increased support with improved sleep quality and less pain.

Pain medication. Pain medication is frequently underprescribed, and should be tailored to the individual's subjective symptoms, not to objective findings. Many clinicians recruit a pain management specialist, but pain can be managed by the primary physician if desired.

Note: All of the following dose recommendations are for adults without hepatic or renal disease; adjustments may be necessary for other populations.

- Acetaminophen, 4000 mg in three or four divided doses, will not completely alleviate pain but is a useful and well-tolerated adjunct. Acetaminophen is often present in combination with other analgesic medications, and careful attention should be paid to the total daily dose to avoid exceeding 4000 mg/day.
- NSAIDs (nonsteroidal anti-inflammatory drugs) (e.g., ibuprofen, naproxen, meloxicam, nabumetone) should be titrated to the maximum dose or as tolerated by upper gastrointestinal symptoms.
- Cox-2 inhibitors (celecoxib) in maximal doses are no stronger than dose-equivalent NSAIDs, but may be better tolerated and thus more effective.
- Tramadol can be added to acetaminophen plus an NSAID or Cox-2 inhibitor before resorting to opioids. Nausea is the most common side effect.
- Topical lidocaine as a cream or patch is sometimes useful for localized areas of pain. Topical capsaicin is of questionable utility, but is safe.
- Skeletal muscle relaxants are useful in combination with the all of the above to treat myofascial spasm. Metaxalone (Skelaxin[®]) may be the least sedating, but all are limited by sedation.
- Tricyclic antidepressants are often effective for neuropathic pain, with additional benefits of mild sedation (sleep is often difficult) and a little mood elevation. Constipation, a common side effect, can be managed with stool softeners and laxatives. Typical doses are nortriptyline (25-150 mg) or trazadone (50-300 mg) every evening.
- Serotonin/norepinephrine receptor inhibitors (SNRIs), such as venlafaxine and duloxetine, also offer combined benefit for depression and neuropathic pain.
- Some anti-seizure medications are also effective for neuropathic pain and can be used in addition to tricyclic antidepressants. All require gradual titration before reaching therapeutic levels. Gabapentin should be titrated as tolerated up to at least 1200 mg three times daily before declaring failure, but is often limited by sedation and/or gastrointestinal side effects. Pregabalin can be dosed twice or three times daily up to a total daily dose of at least 300 mg, and tends to be better tolerated than gabapentin. Topiramate and lamotrigine have also been used successfully.
- Opioids are effective for both myofascial pain and neuropathic pain, but are usually reserved as long as possible. They can be administered in conjunction with all of the above except tramadol. Since they are typically used chronically (or at least several months), the primary formulation should be long acting (e.g., sustained release oxycodone or morphine or topical fentanyl patch) with short-acting forms of the same drug used as needed for breakthrough pain. Routine use of two or more daily doses of a short-acting form should prompt an increase in the long-acting dose or another adjustment to the pain regimen.
- Supplemental magnesium and/or potassium anecdotally may provide some muscle relaxation and pain relief. Diarrhea, nausea, and sedation are the most common side effects. Specific validated dose recommendations do not exist.
- Glucosamine and chondroitin may help to prevent or treat osteoarthritis in the general population. They have not been studied specifically in EDS, but are not contraindicated.

Surgery and other procedures

- Many individuals will have undergone several orthopedic procedures prior to diagnosis. These often include arthroscopic debridement, tendon relocations, capsulorrhaphy, and arthroplasty. The degree of stabilization and pain reduction, overall patient satisfaction, and duration of improvement are variable, but usually less than that in individuals without EDS [Aldridge et al 2003, Rose et al 2004]. In general, orthopedic surgery should be delayed in favor of physical therapy and bracing. When surgery is performed, the patient and physician should cautiously anticipate some improvement but expect less than optimal results. Unlike the classic and vascular types of EDS, the hypermobility type has no increased risk of perioperative complications.
- Prolotherapy, in which saline and/or other irritants are injected in tendons or around joints to induce scar formation and increase stability, has not been objectively studied. It is probably safe, and probably subject to the same limitations as orthopedic surgery.
- Anesthetic/corticosteroid injections for localized areas of pain and inflammation are often helpful, but cannot be repeated indefinitely; "dry needling" without injection of any material sometimes provides similar benefit.
- Anesthetic nerve blocks can provide temporary relief of neuropathic pain. These are sometimes followed by surgical nerve root destruction and/or implantable stimulators (sensory or motor), with variable results.
- Constant intrathecal delivery of anesthetic and/or opioid medication may reduce need for oral/systemic medications, but should only be considered as a last resort.

Bone density. Therapy is the same as for any other individual with low bone density.

Hematologic

- Easy and spontaneous bruising does not require treatment.
- For severe bleeding (e.g., epistaxis, menometrorrhagia) or operative prophylaxis, desmopressin acetate (ddAVP) may be beneficial.

Gastrointestinal

- Gastritis and reflux symptoms may require intensive therapy, including proton pump inhibitor twice daily before meals, high-dose H₂-blocker at bedtime (e.g., famotidine 20-40 mg or ranitidine 150-300 mg), sucralfate one gram four times daily, and over-the-counter acid-neutralizing agents. Other treatable causes, such as *H. pylori* infection, should be investigated. Upper endoscopy is indicated for resistant symptoms, but frequently is normal other than chronic gastritis.
- Delayed gastric emptying should be identified if present and treated as usual with promotility agents (e.g., erythromycin, metoclopramide).
- Irritable bowel syndrome is treated as usual with antispasmodics, antidiarrheals, and laxatives as needed. Tegaserod and lubiprostone are motility enhancers that may be helpful for those with constipation only. Effective March 30, 2007, tegaserod is not available in the United States, but may become available under a restricted use program. Alosetron, for those with diarrhea only, is not currently available except under a restricted use program that is best supervised by a gastroenterologist.

Cardiovascular

- Beta-blockade should be considered for progressive aortic enlargement. Rarely, severe enlargement (>4.5-5.0 cm) requires surgical evaluation.

- Neurally mediated hypotension and postural orthostatic tachycardia are treated as usual, with sodium and water to expand the blood volume, beta-blockade, fludrocortisone, and/or stimulants.

Dental

- Orthodontic and palatal corrections may tend to relapse, requiring prolonged use of a retainer.
- Periodontal disease should be identified and treated.
- Temporomandibular joint laxity and dysfunction are difficult to treat. There are no specific interventions of proven benefit. Intra-oral devices are sometimes helpful. Oral rest (minimization of chewing and talking), local myofascial release, and muscle relaxant medications may be beneficial for acute flares. Surgical intervention is often disappointing and should be considered only as a last resort.

Psychiatric

- Validation of the affected individual's symptoms can be immensely helpful, as many with EDS, hypermobility type have been accused of malingering or diagnosed with primary psychiatric disorders by previous physicians.
- Consumer support groups are available and can be beneficial.
- Depression is a common result of the chronic pain and other complications. Psychological and/or pain-oriented counseling can improve adaptation to and acceptance of these issues and the necessary physical limitations. Antidepressants are also of great benefit. Many individuals initially resist a diagnosis of or therapy for depression because of concern that their problems are being written off as purely psychiatric.

Prevention of Primary Manifestations

Improved joint stability may be achieved by low-resistance exercise to increase muscle tone (subconscious resting muscle contraction, as opposed to voluntarily recruited muscle strength). Examples include walking, bicycling, low-impact aerobics, swimming or water exercise, and simple range-of-motion exercise without added resistance. Progress should be made by increasing repetitions, frequency, or duration, not resistance. It may take months or years for significant progress to be recognized.

Wide grip writing utensils can reduce strain on finger and hand joints. An unconventional grasp of a writing utensil, gently resting the shaft in the web between the thumb and index finger and securing the tip between the distal interphalangeal joints or middle phalanges of the index and third fingers (rather than using the tips of the fingers), results in substantially reduced axial stress to the interphalangeal, metacarpophalangeal, and carpometacarpal joints. These adjustments frequently result in marked reduction of pain in the index finger and at the base of the thumb.

Prevention of Secondary Complications

Calcium (500-600 mg twice daily), vitamin D (400 units daily), and low-impact weight bearing exercise should be encouraged to maximize bone density.

Surveillance

DEXA should be repeated every other year if bone loss is confirmed.

The long-term prognosis for aortic enlargement, and therefore the interval for repeating echocardiograms, is currently unknown. In adults with a normal aortic root diameter, it is reasonable to repeat the echocardiogram approximately every five years. In children and adolescents with a normal aortic root diameter, it is the author's practice to repeat every one to three years until adulthood. If the aortic root diameter is increased or accelerating faster than body surface area, more frequent monitoring is appropriate.

Agents/Circumstances to Avoid

Joint hyperextension must be avoided. Individuals with EDS, hypermobility type usually need to be educated about the normal range of joint extension and cautioned not to exceed it.

Resistance exercise, including elastic resistance bands, can exacerbate joint instability and pain.

Isometric exercise can also be problematic if too much force (resistance) is applied.

High-impact activity increases the risk of acute subluxation/dislocation, chronic pain, and osteoarthritis. Some sports, such as football, are therefore contraindicated. However, most sports and activities are acceptable with appropriate precautions.

Chiropractic adjustment is not strictly contraindicated, but must be performed cautiously to avoid iatrogenic subluxations or dislocations.

Crutches, canes, and walkers should be used cautiously as they put increased stress on the upper extremities.

Testing of Relatives at Risk

First-degree relatives are each at 50% risk of having EDS, hypermobility type, and may wish to undergo formal clinical assessment. Those without significant clinical manifestations may not benefit directly from knowing that they are affected, but may benefit from knowing that their children are at risk. Evaluation of young children (before age ~5 years) is difficult because of the normal joint laxity in that age group.

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

Therapies Under Investigation

Search [ClinicalTrials.gov](https://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

Vitamin C is a cofactor for cross-linking of collagen fibrils. Supplementation with 500 mg daily may improve some of the manifestations. Higher doses are likely excreted and offer no additional clinical benefit.

Losartan is under investigation for treatment and prophylaxis of aortic aneurysm in Marfan syndrome and Loeys-Dietz syndrome. If proven safe and effective, it may be reasonable to use it similarly for individuals with EDS, hypermobility type who have aortic enlargement.

Genetics clinics are a source of 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 (below) 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.

Mode of Inheritance

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

Risk to Family Members

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

Parents of a proband

- Most individuals diagnosed with EDS, hypermobility type have an affected parent, although a careful history and examination of the parents is often necessary to recognize that, despite absence of serious complications, one (and sometimes both) has current or prior history of joint laxity, easy bruising, and soft skin.
- A proband with EDS, hypermobility type may have the disorder as the result of a *de novo* gene mutation. The proportion of cases caused by *de novo* mutations is unknown.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include a careful history and examination seeking current or prior history of joint laxity, easy bruising, and soft skin.

Note: Although most individuals diagnosed with EDS, hypermobility type 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 the 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.

Offspring of a proband. Each child of an individual with EDS, hypermobility type has a 50% chance of inheriting the mutation. However, because of marked clinical variability, it is difficult to predict severity among affected offspring.

Other family members of a proband. The risk to other family members depends upon the genetic status of the proband's parents. If a parent is found to be affected, his or her family members are at risk.

Related Genetic Counseling Issues

It is worthwhile to emphasize to affected individuals and family members that EDS, hypermobility type does not evolve into any of the other types, either in the affected individual or in their offspring, and that the hypermobility type does not confer increased risk of early mortality.

Considerations in families with an apparent *de novo* mutation. When neither parent of a proband with an autosomal dominant condition has clinical evidence of the disorder, it is likely that the proband has a *de novo* mutation. However, possible non-medical explanations including alternate paternity or maternity (i.e., with assisted reproduction) or undisclosed adoption could also be explored.

Family planning. The optimal time for determination of genetic risk 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 molecular genetic testing is available on a research basis only, or not all of the genes in which disease-causing mutations occur have been identified. See DNA Banking for a list of laboratories offering this service.

Prenatal Testing

Because the gene(s) and mutation(s) responsible for the majority of cases of Ehlers-Danlos syndrome, hypermobility type have not been identified, prenatal testing is not available.

No laboratories offering molecular genetic testing for prenatal diagnosis of EDS, hypermobility type caused by *TNXB* are listed in the GeneTests Laboratory Directory. However, prenatal testing may be available for families in which the *TNXB* disease-causing mutation has been identified. For laboratories offering custom prenatal testing, see [Testing](#).

Preimplantation genetic diagnosis (PGD) may be available for families in which a *TNXB* disease-causing mutation have been identified. For laboratories offering PGD, see

[Testing](#).

Molecular Genetics

Information in the Molecular Genetics tables is current as of initial posting or most recent update. —ED.

Table A. Molecular Genetics of Ehlers-Danlos Syndrome, Hypermobility Type

Gene Symbol	Chromosomal Locus	Protein Name
<i>TNXB</i>	6p21.3	Tenascin-X

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.

Table B. OMIM Entries for Ehlers-Danlos Syndrome, Hypermobility Type

130020	EHLERS-DANLOS SYNDROME, TYPE III
600985	TENASCIN XB; TNXB

Table C. Genomic Databases for Ehlers-Danlos Syndrome, Hypermobility Type

Gene Symbol	Entrez Gene	HGMD
<i>TNXB</i>	7148 (MIM No. 600985)	TNXB

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

Molecular Genetic Pathogenesis

A very small number of individuals with Ehlers-Danlos syndrome (EDS), hypermobility type have demonstrable haploinsufficiency of tenascin X (*TNXB*). In most cases the gene(s) is/are unknown.

Normal allelic variants: *TNXB* is a 39-exon gene spanning 65 kb. It lies in an antisense orientation to and overlaps the final exon of the steroid 21-hydroxylase gene (*CYP21B*), and the entire complex is tandemly duplicated as a pseudogene (*TNXA* and *CYP21A*) that predisposes to gene conversion and/or deletion events. See 21-Hydroxylase-Deficient Congenital Adrenal Hyperplasia and OMIM entry 600985 for more detail.

Pathologic allelic variants: Only three mutations have been described. One was a large (30-kb) deletion, one a 2-bp deletion in exon 8 resulting in a premature stop codon, and one a 2-bp insertion in exon 3 resulting in a premature stop codon. All result in biochemical haploinsufficiency in the heterozygous state.

Normal gene product: Tenascin X is an extracellular matrix glycoprotein of uncertain specific function produced primarily by dermal and skeletal muscle fibroblasts. Tenascins are important in cell adhesion and spreading [Chiquet-Ehrismann & Tucker 2004].

Abnormal gene product: Complete deficiency of tenascin X results in abnormal dermal elastic fibers and reduced quantity of structurally normal dermal collagen fibers [Zweers et al 2004].

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. Information that appears in the Resources section of a *GeneReview* is current as of initial posting or most recent update of the *GeneReview*. Search GeneTests for this disorder and select **Resources** for the most up-to-date Resources information.—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

83 Grapevine Road

Bolton L7E 2M5
 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

Medline Plus

Ehler-Danlos Syndrome

National Library of Medicine Genetics Home Reference

Ehlers-Danlos syndrome

Ehlers-Danlos Support Group

PO Box 337
 Aldershot GU12 6WZ
 United Kingdom
Phone: 01252 690940
Email: director@ehlers-danlos.org
 www.ehlers-danlos.org

References

Medical Genetic Searches: A specialized PubMed search designed for clinicians that is located on the PubMed Clinical Queries page. [PubMed](#)

Published Statements and Policies Regarding Genetic Testing

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

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Suggested Readings

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Chapter Notes

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