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Ehlers-Danlos Syndrome Type IV

Synonyms: EDS Type IV; Ehlers-Danlos Syndrome, Vascular Type

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Summary

Disease characteristics. Ehlers-Danlos syndrome type IV (EDS type IV) is characterized by thin, translucent skin; easy bruising; characteristic facial appearance (in some individuals); and arterial, intestinal, and/or uterine fragility. Vascular dissection or rupture, gastrointestinal perforation, or organ rupture are the presenting signs in the majority of adults identified to have EDS type IV. Arterial rupture may be preceded by aneurysm, arteriovenous fistulae, or dissection but also may occur spontaneously. Neonates may present with clubfoot and/or congenital dislocation of the hips. In childhood, inguinal hernia, pneumothorax, and recurrent joint subluxation or dislocation can occur. Pregnancy for women with EDS type IV has as much as a 12% risk for death from peripartum arterial rupture or uterine rupture. One-fourth of individuals with EDS type IV who have undergone laboratory testing to confirm their diagnosis have experienced a significant medical problem by age 20 years and more than 80% by age 40 years. The median age of death in this reviewed population was 48 years.

Diagnosis/testing. The diagnosis of EDS type IV is based on clinical findings and confirmed by identification of a causative mutation in *COL3A1*, the only gene in which mutations are known to cause EDS type IV. Sequence analysis detects 98% of mutations, while rare exonic deletions are detected by *COL3A1* deletion/duplication analysis or collagen screening and cDNA amplification. Analysis of collagens produced by cultured fibroblasts ("biochemical studies") from affected individuals can demonstrate abnormalities of type III procollagen production, intracellular retention, reduced secretion, and/or altered mobility in cells from some individuals in which no mutation was detected by genomic sequencing.

Management. *Treatment of manifestations:* Affected individuals are instructed to seek immediate medical attention for sudden, unexplained pain. Treatment may include surgery for arterial or bowel complications/rupture.

Surveillance: May include periodic arterial screening by magnetic resonance imaging or computed tomographic imaging with or without venous contrast.

Evaluation of relatives at risk: The genetic status of at-risk relatives should be clarified through clinical evaluation and molecular genetic testing.

Pregnancy management: Pregnant women should be followed in a high-risk obstetric program.

Agents/circumstances to avoid: Trauma (contact sports, heavy lifting, and heavy weight training); arteriography should be used with great caution and only to identify life-threatening sources of bleeding prior to surgical

intervention because of the risk of vascular injury.

Other: A MedicAlert® bracelet should be worn.

Genetic counseling. EDS type IV is inherited in an autosomal dominant manner. About 50% of affected individuals have inherited the *COL3A1* mutation from an affected parent, and about 50% of affected individuals have a *de novo* disease-causing mutation. Each child of an affected individual has a 50% chance of inheriting the mutation and developing the disorder. Both parental somatic/germline mosaicism and parental isolated germline mosaicism have been reported. Prenatal testing for pregnancies at increased risk is possible in families in which the disease-causing mutation in *COL3A1* has been identified. In rare families in which only the biochemical abnormality is known, analysis of cultured CVS cells can substitute.

Diagnosis

Clinical Diagnosis

Diagnostic criteria and standardized nomenclature for the Ehlers-Danlos syndromes (EDSs) were suggested by a medical advisory group in a conference sponsored by the Ehlers-Danlos National Foundation (US) and the Ehlers-Danlos Support Group (UK) at Villefranche in 1997 [Beighton et al 1998].

Diagnostic criteria for Ehlers-Danlos syndrome type IV (EDS type IV) are modified here to reflect the authors' experience.

The combination of **any two of the major diagnostic criteria** should have a high specificity for EDS type IV; DNA testing is strongly recommended to confirm the diagnosis. The presence of **two or more minor criteria** should lead to consideration of the diagnosis of EDS type IV but is not sufficient to establish the diagnosis.

Major diagnostic criteria for EDS type IV include:

- Arterial rupture
- Intestinal rupture
- Uterine rupture during pregnancy
- Family history of EDS type IV

Minor diagnostic criteria for EDS type IV include:

- Thin, translucent skin (especially noticeable on the chest/abdomen)
- Characteristic facial appearance (thin lips and philtrum, small chin, thin nose, large eyes)
- Acrogeria (an aged appearance to the extremities, particularly the hands)
- Arteriovenous carotid-cavernous sinus fistula
- Hypermobility of small joints
- Tendon/muscle rupture
- Early-onset varicose veins
- Pneumothorax/pneumohemothorax
- Easy bruising (spontaneous or with minimal trauma)

- Chronic joint subluxations/dislocations
- Congenital dislocation of the hips
- Talipes equinovarus (clubfoot)
- Gingival recession

Testing

Biochemical (protein-based) testing. Biochemical testing for EDS type IV requires cultured dermal fibroblasts. Proteins synthesized by these cells are biosynthetically labeled with radio-labeled proline, and assessed by sodium dodecyl-sulfate polyacrylamide gel electrophoresis (SDS-PAGE). The amount of type III procollagen synthesized, the quantity secreted into the medium, and the electrophoretic mobility of the constituent chains are assessed.

Analysis of type III procollagen synthesized by cultured cells can identify abnormalities in synthesis and mobility of type III collagen chains. Such testing remains a valuable resource to confirm mRNA and protein consequences when a unique sequence variant is identified and to look for protein abnormalities in an individual with convincing phenotype but an apparently normal sequence of *COL3A1*. Rare small multiexonic deletions not detected by deletion/duplication analysis (e.g., MLPA) may be identified using cDNA sequencing.

Molecular Genetic Testing

Gene. *COL3A1* is the only gene in which mutations are known to cause EDS type IV.

Clinical testing

- **Sequence analysis.** Direct sequence analysis of the coding regions and adjacent splice sites of *COL3A1* using DNA extracted from a blood sample or other source of genomic DNA identifies a mutation in over 95% of individuals with EDS type IV. The majority (~2/3) of identified mutations result in substitution of other amino acids for glycine residues in the $[Gly\text{-}X\text{-}Y]_{343}$ triplets of the triple helical domain. Most of the remaining mutations affect splice sites and usually result in exon skipping, but other more complex outcomes can occur. About 4% of identified mutations lead to mRNA instability or to failure of chain association in the products of the mutant allele [Schwarze et al 2001, Leistritz et al 2010].
- **Deletion/duplication analysis** can identify exon and multiexon *COL3A1* deletions if the target exons are in the amplification set. About 2% of all individuals with EDS type IV have a genomic deletion. We have confirmed that although found by other methods, these could be detected by deletion/duplication analysis such as MLPA. The low frequency of genomic deletions is consistent with the failure to detect a deletion after routine screening (by MLPA) of approximately 100 specimens submitted for *COL3A1* clinical sequencing studies [Boston University School of Medicine - Human Genetics DNA Diagnostic Laboratory genetic counselors, personal communication]. One 3.5-Mb contiguous gene deletion that includes *COL3A1* was identified by MLPA [Meienberg et al 2010].

Table 1. Summary of Molecular Genetic Testing of EDS Type IV

Gene Symbol	Test Method	Mutations Detected	Mutation Detection Frequency by Test Method [1]
COL3A1	Sequence analysis	Sequence variants [2]	>95%
	Deletion / duplication analysis [3]	Exonic or whole gene-deletions	~2% [4]

1. The ability of the test method used to detect a mutation that is present in the indicated gene

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

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

4. Genomic deletions are rare, although splice site mutations that lead to exon skipping are frequently seen. The majority of exon-skipping events have been confirmed by cDNA amplification and sequencing. MLPA should be effective in detecting single- or multiple-exon deletion events if the target exon is in the MLPA set.

Interpretation of test results

- For issues to consider in interpretation of sequence analysis results, click here.
- For issues related to the value of protein-based testing see Biochemical (protein-based) testing.

Testing Strategy

To confirm/establish the diagnosis in a proband

- **Sequence analysis** of *COL3A1* confirms the clinical diagnosis of EDS type IV over 95% of the time. Sequence analysis identifies variants of unknown significance, the role of which may be defined by biochemical (protein-based) testing.
- **Deletion/duplication analysis**. If a mutation is not detected on sequence analysis of genomic DNA, deletion/duplication analysis may be indicated, particularly in instances when sequencing does not identify heterozygous sequence variants and the phenotype is compelling. To date, such deletions are rare (<2%) in *COL3A1*.
- **Biochemical (protein-based) testing.** Testing of type III procollagen synthesized by cultured cells from a skin biopsy is the recommended assay when a mutation is not identified by sequence analysis or when a sequence variant of unknown clinical significance is found. Such testing may confirm mRNA and protein consequences of a variant of unknown significance or may identify a type III collagen protein abnormality, indicating that the mutation was missed as a result of a technical problem (e.g., mutation is masked by location under a primer or presence of a multiexonic deletion).

Predictive testing for at-risk asymptomatic adult family members requires prior identification of the disease-causing mutation in the family.

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

Genetically Related (Allelic) Disorders

Ehlers-Danlos syndrome, hypermobility type (EDS type III). A single report of a family with clinical features of EDS type III and a *COL3A1* mutation typically associated with the EDS type IV (NM_000090.3:c.2410G>A (p.Gly804Ser) or Gly637Ser in the triple helical domain) [Narcisi et al 1994] led to the suspicion of a causative relationship between *COL3A1* mutations and EDS type III; however, neither biochemical studies of collagen synthesis nor *COL3A1* genomic DNA sequence analysis have identified a type III collagen defect in any other individuals with the clinical diagnosis of EDS type III. Given the relatively young ages of most individuals in the reported family and

sparse history, reassessment is warranted.

Familial aortic aneurysm. A *COL3A1* glycine substitution mutation was identified in one family described with familial aortic aneurysm, but clinically more consistent with EDS type IV, and in another family with aortic aneurysm. In spite of this report, existence of a subset of individuals with a *COL3A1* mutation giving rise to the phenotype of familial aortic aneurysm in the absence of other findings of EDS type IV seems unlikely [Author, personal observation].

Clinical Description

Natural History

A retrospective review of the health history of more than 400 individuals with Ehlers-Danlos syndrome (EDS) type IV confirmed by biochemical and/or molecular genetic testing delineated the natural history of the disorder [Pepin et al 2000]. Among individuals ascertained as a result of complications, 25% had experienced a significant medical complication by age 20 years and more than 80% by age 40 years. In a population ascertained on the basis of major complications or clinical criteria alone, in which all had evidence of abnormal type III procollagen production in cultured dermal fibroblasts, the median age of death is 48 years.

As of 2010, more than 500 *COL3A1* mutations have been identified by molecular testing in the authors' laboratory and almost 200 others have been reported. Within this group a subpopulation of 3%-4% have haploinsufficiency mutations. Review of clinical histories of the *COL3A1* probands and family members reveals a 15-year delay in onset of complications, similarly improved life expectancy, and paucity of both obstetric and bowel complications [Leistritz et al 2010].

Children. Approximately 12% of neonates with EDS type IV have clubfoot, and 3% have congenital dislocation of the hips. Rare infants have evidence of amniotic bands including a small number with limb deficiencies.

In childhood, inguinal hernia, pneumothorax, and recurrent joint dislocation or subluxation are described.

Affected individuals often have a lifelong history of easy bruising.

Most children with EDS type IV have few major complications; and, in families with a negative family history, the disorder is often unrecognized in childhood.

Adults. Vascular rupture or dissection and gastrointestinal perforation or organ rupture are the presenting signs in 70% of adults with missense and exon-skipping mutations of *COL3A1*. Such complications are dramatic and often unexpected, presenting as sudden death, stroke and its neurologic sequelae, acute abdomen, retroperitoneal bleeding, uterine rupture at delivery, and/or shock. The average age for the first major arterial or gastrointestinal complication is 23 years in this group.

Individuals with haploinsufficiency mutations may present with arterial events (none yet are described with bowel-or pregnancy-related catastrophes); the average age of first event in this group is 37 years.

Vascular complications include rupture, aneurysm, and/or dissection of major or minor arteries. Arterial rupture may be preceded by aneurysm, arteriovenous fistulae, or dissection, or may occur spontaneously. The sites of arterial rupture are the thorax and abdomen (50%), head and neck (25%), and extremities (25%). The clinical presentation depends on the location of the arterial event.

Rupture of the gastrointestinal (GI) tract occurs in about 25% of affected individuals with missense mutations. To date, such GI events have not been documented in the families with haploinsufficiency mutations. The majority of GI perforations occur in the sigmoid colon. Ruptures of the small bowel and stomach have been reported, though

infrequently. Bowel rupture is rarely lethal (3%) [Pepin et al 2000]. Recurrent bowel rupture proximal to the first sigmoid tear is common.

Surgical intervention for bowel rupture is necessary and usually lifesaving. Surgical re-anastomosis can generally be accomplished. Complications during and following surgery are related to tissue and vessel friability, which result in recurrent arterial or bowel tears, fistulae, poor wound healing, and suture dehiscence. Individuals who survive a first complication may experience recurrent rupture. The timing and site of repeat rupture cannot be predicted by the first event.

Rare complications include organ rupture that may involve the heart (with ventricular rupture), the spleen, or the liver [Pepin et al 2000, Ng & Muiesan 2005].

Keratoconus [Kuming & Joffe 1977], periodontal disease, and venous varicosities have been reported [Tsipouras et al 1986].

Pregnancy for women with EDS type IV has as much as a 12% risk for death from peripartum arterial rupture or uterine rupture [Pepin et al 2000].

Genotype-Phenotype Correlations

To date, the only clear genotype-phenotype correlations are the 15-year delay in onset of complications, decreased penetrance, and increased life expectancy in individuals with haploinsufficiency mutations, and the higher frequency of acrogeria in individuals with mutations that alter the carboxyl-terminal quarter of the triple helical domain of the chains of type III procollagen [Leistritz et al 2010].

Penetrance

In families identified on the basis of clinical complications, penetrance of the EDS type IV phenotype appears to be close to 100% with a missense or exon-skipping mutation; the age at which the mutation becomes penetrant may vary.

Nomenclature

The following terms have been used to describe EDS type IV:

- **Status dysvascularis** was introduced by Sack [1936]; never used extensively.
- **Familial acrogeria,** used by Gottron [1940], probably included some individuals with EDS type IV.
- **Sack-Barabas syndrome** or the **Sack-Barabas type of Ehlers-Danlos syndrome** was used after Barabas [1967] introduced the disorder to the English language literature.
- **Ehlers-Danlos syndrome, vascular type** came into widespread use following the shift from a numerical classification of EDS to a descriptive one [Beighton et al 1998].

Prevalence

There are no good current estimates of the prevalence of EDS type IV in any population. About 1500 affected individuals in the United States have been identified on the basis of biochemical and genetic testing and analysis of family pedigrees [Author, personal observation]. This leads to a minimum estimate of the prevalence of about 1:200,000. The decreased frequency of certain classes of mutations suggests that the overall prevalence of individuals with mutations in *COL3A1* (see Molecular Genetics) could approach that of individuals with mutations in *COL1A1*, which is estimated to be close to 1:50,000.

Because many families with EDS type IV are identified only after a severe complication or death, it is likely that

individuals/families with *COL3A1* mutations with a mild phenotype do not come to medical attention and, therefore, go undetected. In addition, because of the perceived rarity of the disorder, it is rarely considered and non-vascular complications rarely raise diagnostic suspicion of EDS type IV.

Differential Diagnosis

Other forms of Ehlers-Danlos syndrome (EDS) should be considered in individuals with easy bruising, joint hypermobility, and/or chronic joint dislocation who have normal collagen III biochemical studies or genetic analysis of *COL3A1*. The disorders in which clinical findings overlap with EDS type IV include the following:

- **Ehlers-Danlos syndrome, classic type** is an autosomal dominant disorder characterized by soft, doughy, stretchy skin; abnormal scars; and significant large-joint hypermobility without accompanying blood vessel, bowel, or organ rupture. The diagnosis is based on clinical and family history findings. More than half of individuals with EDS, classic type, have an identifiable mutation in *COL5A1* or *COL5A2*.

- **Ehlers-Danlos syndrome VI (kyphoscoliotic form)** is an autosomal recessive disorder characterized by progressive scoliosis, hypotonia, easy bruising and tissue fragility, and fragility of the globe. Vascular rupture may be a feature of this type of EDS. EDS, kyphoscoliotic form is caused by mutations in *PLOD1*, which encodes lysyl hydroxylase 1 (procollagen-lysine, 2-oxoglutarate 5-dioxygenase 1). The diagnosis of EDS, kyphoscoliotic form relies on the demonstration of an increased ratio of deoxypyridinoline to pyridinoline crosslinks in urine measured by high pressure liquid chromatography (HPLC) and identification of a mutation in *PLOD1*.

- **Ehlers-Danlos syndrome VIII (periodontal form)** is a rare disorder including features of the **classic type** with the additional findings of early periodontal friability. Recent studies suggest that a gene for a variety of this type of EDS is located on the short arm of chromosome 12.

- **Isolated arterial aneurysm** is usually NOT the result of a type III collagen defect. Familial forms of arterial aneurysm have been linked to at least three different loci in addition to the six identified genes (see Thoracic Aortic Aneurysms and Aortic Dissections).

- **Loeys-Dietz syndrome (LDS)** is an autosomal dominant disorder characterized by vascular findings (cerebral, thoracic, and abdominal arterial aneurysms and/or dissections) and skeletal manifestations (pectus excavatum or pectus carinatum, scoliosis, joint laxity, arachnodactyly, talipes equinovarus). Approximately 75% of affected individuals have LDS type I with craniofacial manifestations (ocular hypertelorism, bifid uvula/cleft palate, craniosynostosis); approximately 25% have LDS type II with cutaneous manifestations (velvety and translucent skin; easy bruising; widened, atrophic scars). LDSI and LDSII form a clinical continuum. The natural history of LDS is characterized by aggressive arterial aneurysms (mean age at death 26.1 years) and high incidence of pregnancy-related complications including death and uterine rupture.

  The diagnosis of LDS is based on characteristic clinical findings in the proband and family members and molecular genetic testing of *TGFBR1* and *TGFBR2*, the only two genes in which causative mutations have been found.

Other causes of arterial rupture include localized trauma and collagen vascular disease.

- **Polycystic kidney disease, autosomal dominant** is characterized by progressive cyst development and bilaterally enlarged polycystic kidneys. Cysts also occur in liver, seminal vesicles, pancreas, and arachnoid membrane. Non-cystic abnormalities include intracranial aneurysms and dolichoectasias, dilatation of the aortic root and dissection of the thoracic aorta, mitral valve prolapse, and abdominal wall hernias. The renal

manifestations of ADPKD include renal function abnormalities, hypertension, renal pain, and renal insufficiency. ADPKD is caused by mutations in *PKD1* in 85% of affected individuals; in 15% of individuals, mutations in *PKD2* are causative. This disorder should be considered in individuals with intracranial aneurysm.

- **Marfan syndrome** should be considered if the presenting vascular complication is an aortic aneurysm or dissection. EDS type IV and Marfan syndrome can be distinguished relatively easily on physical examination. Individuals with Marfan syndrome typically have dolichostenomelia and arachnodactyly, lens dislocation, and dilatation or aneurysm of only the aorta. Marfan syndrome is a clinical diagnosis based on family history and the observation of characteristic findings in multiple organ systems. It is caused by mutations in *FBN1*.

- Gastrointestinal entities to be considered in individuals of any age with large or small bowel rupture are perforated diverticulitis, irritable bowel disease, or inflamed Meckel's diverticulum. Isolated gastrointestinal bleeding, as seen in pseudoxanthoma elasticum and hereditary hemorrhagic telangectasia, is not part of the usual presentation of EDS type IV.

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

Management

Evaluations Following Initial Diagnosis

Currently, no consensus exists regarding the appropriate extent of evaluation at the time of initial diagnosis.

Approach to a vascular evaluation depends on the age of the individual and the circumstances in which the diagnosis is made.

Because of the risk of asymptomatic aneurysm/dissection, initial visualization of the arterial tree is commonly undertaken; the approach employed varies by region and by institution (see Surveillance).

No gastrointestinal factors are known to increase the risk of bowel rupture, thus negating the need for initial invasive GI evaluation.

Treatment of Manifestations

Surgical intervention may be life-saving in the face of bowel rupture, arterial rupture, or organ rupture (e.g., the uterus in pregnancy). When surgery is required for treatment, it is appropriate to target the approach and minimize surgical exploration because of the risk of inadvertent damage to other tissues [Oderich et al 2005]. In general, surgical procedures are more likely to be successful when the treating physician is aware of the diagnosis of EDS type IV and its associated tissue fragility.

Prompt surgical intervention of bowel rupture is essential to limit the extent of infection and facilitate early restoration of bowel continuity. Death from bowel rupture is uncommon because intervention is generally effective. Bowel continuity can be restored successfully in most instances, usually three to six months after the initial surgery.

The recurrence of bowel tears proximal to the original site and the risk of complications resulting from repeat surgery have led some to recommend partial colectomy to reduce the risk of recurrent bowel rupture. Some physicians and affected individuals consider total colectomy as a prophylactic measure to avoid recurrent bowel complications and the need for repeat surgery [Fuchs & Fishman 2004].

Affected individuals should be instructed to seek immediate medical attention for sudden, unexplained pain.

A MedicAlert® bracelet should be worn.

Surveillance

The use of surveillance of the arterial tree assumes that effective interventions will decrease the risk of arterial dissection or rupture and prolong life. At a time when an open surgical approach was the only alternative, the benefit of surveillance could not be established. As endovascular approaches to management of aneurysms and dissection become more available, intervention is considered earlier and surveillance is seen to have greater benefit. There are, however, no published data that assess the efficacy of screening strategies to identify the regions in the arterial vasculature at highest risk; conversely, there are examples in which regions of concern in the arterial vasculature failed to progress and arterial rupture occurred at other more distant sites. Thus, the benefit of controlled studies cannot be overemphasized.

If undertaken, the noninvasive imaging such as sonography, MR or CT angiography with or without venous contrast has been documented to identify aneurysms, dissections, and vascular ruptures.

Conventional arterial angiography (with contrast injection) should be discouraged because it has been associated with added *de novo* complications [Zilocchi et al 2007]. Arterial tear/dissection may result at the site of entry of the catheter; furthermore, injection pressure may lead to arterial aneurysms. Arteriography is currently best used as part of a planned interventional procedure, such as coil embolization or stenting of bleeding arteries.

Agents/Circumstances to Avoid

Trauma. Because of inherent tissue fragility, it is prudent for individuals with EDS type IV to avoid collision sports (e.g., football), heavy lifting, and weight training. Of note, no evidence suggests that moderate recreational exercise is detrimental.

Elective surgery. Increased tissue fragility results in a higher risk of surgical complications; thus, elective surgery for individuals with EDS type IV is discouraged. In general, avoidance of surgery in favor of more conservative management is advised. For example, bleeding from a small vessel into a confined space is often best treated conservatively.

Arteriograms. Because arterial tear/dissection may result at the site of entry of the catheter and at sites of high pressure injection, arteriograms are not recommended and the use of CTA, MRA, and ultrasonography should be considered for routine surveillance.

Routine colonoscopy should be avoided because of the risks of bowel perforation by the instrument and secondary to insufflation. Routine colonoscopy for cancer screening should be replaced with noninvasive measures. Virtual colonoscopy, which also involves insufflation, may have similar complications. In the face of a family history of cancer, standard or emerging strategies of surveillance may be of benefit.

Evaluation of Relatives at Risk

The genetic status of at-risk relatives can be clarified by molecular genetic testing if the disease-causing mutation in the family is known. For those found to have the family-specific mutation, management is the same as for individuals identified through clinical findings.

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

Pregnancy Management

It is prudent to follow pregnant women with EDS type IV in a high-risk obstetrical program.

It is not known if elective caesarian section decreases the risk of mortality and vaginal and cervical tears and these benefits outweigh the associated morbidity.

Educating the pregnant woman as to possible complications and the need for close monitoring is recommended.

Therapies Under Investigation

A recently published clinical trial of the efficacy of a cardioselective β-blocker with β-2 agonist vasodilatory properties (celiprolol) in reducing risk of arterial rupture or dissection concluded that there was a benefit: a reduced number of arterial events (rupture or dissection, fatal or not) was reported in the treatment group. Although the study was directed to measure benefit in individuals with EDS type IV, randomization to treatment or control group was undertaken prior to mutation characterization. The treated and untreated groups with mutations differed in size and age distribution so that it is difficult to determine if there is a measurable benefit [Ong et al 2010].

Search ClinicalTrials.gov for access to information on clinical studies for a wide range of diseases and conditions.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members. This section is not meant to address all personal, cultural, or ethical issues that individuals may face or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Ehlers-Danlos syndrome (EDS) type IV is an autosomal dominantly inherited disorder but almost half of the newly ascertained affected individuals have new mutations.

Risk to Family Members

Parents of a proband

- About 50% of affected individuals have inherited the *COL3A1* mutation from an affected parent, and about 50% of affected individuals have a *de novo* disease-causing mutation.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* mutation include physical examination and molecular genetic testing as the rate of parental mosaicism in families with EDS type IV may be as high as 20%.
- Parental somatic mosaicism for *COL3A1* mutations that includes the germline has been documented in 11 families in which affected individuals have been born to unaffected parents; mosaicism that is apparently limited to the germline has been reported in two families [Byers et al 2003, Palmeri et al 2003].

Note: Although many individuals diagnosed with EDS type IV have an affected parent, the family history may appear to be negative because of failure to recognize the disorder in family members or later onset of the disease in the affected parent.

Sibs of a proband

- The risk to the sibs depends on the genetic status of the proband's parents.

- If a parent of the proband is affected, the risk to each sib is 50%.
- If the parents are clinically unaffected and the proband's disease-causing mutation cannot be detected in DNA extracted from the leukocytes of either parent, there remains a chance that one parent is mosaic in his or her germline. In this situation the recurrence risk is probably about 1%.

Offspring of a proband. Each child of an individual with EDS type IV has a 50% chance of inheriting the mutation and developing the disorder.

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

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

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

Family planning

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

Testing of at-risk asymptomatic individuals younger than age 18 years. In the case of EDS type IV the benefits of testing individuals younger than age 18 years include: (1) elimination of concern for those children who do not have the *COL3A1* mutant allele identified; and (2) improved surveillance, awareness of treatment for potential complications, and appropriate restriction of high-impact sports for those with the mutant allele.

Testing of apparently asymptomatic individuals younger than age 18 years for disorders in which most of the complications occur in adulthood raises ethical considerations. Consensus holds that individuals at risk for adult-onset disorders should not be tested during childhood in the absence of symptoms, if the testing can have no positive consequences such as intervention or improved surveillance. The principal arguments against testing asymptomatic individuals who are younger than age 18 years are that it removes their choice to know or not know this information, it raises the possibility of stigmatization within the family and in other social settings, and it could have serious educational and career implications. See also the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Society of Human Genetics and American College of Medical Genetics points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. In the authors' experience the majority of families choose to test, even after discussion of the considerations mentioned above [Authors, personal experience].

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

Prenatal Testing

Molecular genetic 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 to 18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. The disease-causing allele of an affected family member must be identified before prenatal testing can be performed.

Biochemical testing. Prenatal diagnosis is possible for pregnancies at increased risk in families in which the underlying biochemical abnormality of type III collagen has been identified. Prenatal diagnosis using the biochemical assay can be performed only on cultured cells obtained by chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. In most instances molecular genetic testing is preferable, more rapid, and available for a wider range of mutations.

Note: Gestational age is expressed as menstrual weeks calculated either from the first day of the last normal menstrual period or by ultrasound measurements.

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

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Association Francaise des Syndrome d'Ehlers Danlos**
  34 rue Léon Joulin
  Turns 37 000
  France
  Email: contact@afsed.com
  www.afsed.com
- **Canadian Ehlers Danlos Association**
  88 De Rose Avenue
  Bolton Ontario L7E 1A8
  Canada
  Phone: 905-951-7559
  Fax: 905-761-7567
  Email: ceda@rogers.com
- **Ehlers-Danlos National Foundation**
  1760 Old Meadow Road
  Suite 500
  McLean VA 22102
  Phone: 703-506-2892
  Email: ednfstaff@ednf.org
  www.ednf.org
- **Ehlers-Danlos Support Group**
  PO Box 337
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- **National Library of Medicine Genetics Home Reference**
  Ehlers-Danlos syndrome
- **Medline Plus**
  Ehler-Danlos Syndrome
- **National Registry of Genetically Triggered Thoracic Aortic Aneurysms and Cardiovascular Conditions (GenTAC)**
  Phone: 800-334-8571 ext 24640
  Email: gentac-registry@rti.org
  GenTAC

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. Ehlers-Danlos Syndrome Type IV: Genes and Databases

Gene Symbol	Chromosomal Locus	Protein Name	Locus Specific	HGMD
COL3A1	2q32.2	Collagen alpha-1(III) chain	Ehlers-Danlos Syndrome Variant Database COL3A1 Database of osteogenesis imperfecta and type III collagen mutations	COL3A1

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

Table B. OMIM Entries for Ehlers-Danlos Syndrome Type IV (View All in OMIM)

120180	COLLAGEN, TYPE III, ALPHA-1; COL3A1
130050	EHLERS-DANLOS SYNDROME, TYPE IV, AUTOSOMAL DOMINANT

Normal allelic variants. The *COL3A1* cDNA comprises 51 exons distributed over 44 kb of genomic DNA (reference sequence NM_000090.3). The Database of Human Type I and Type III Collagen Mutations (www.le.ac.uk/genetics/collagen) provides a list of known variants.

Pathologic allelic variants. More than 600 mutations in *COL3A1* that result in a disease-causing phenotype have been identified.

The majority of identified mutations result in single amino acid substitutions for glycine in the GLY-X-Y repeat of the triple helical region of the type III collagen molecule. About one third of the known mutations occur at splice sites, and most result in exon skipping. A smaller number of splice mutations lead to the use of cryptic splice sites with partial exon exclusion or intron inclusion. The vast majority of exon-skipping splice site mutations have been

identified at the 5' donor site, with very few found at the 3' splice site. Several partial gene deletions have been reported as well. Less common are mutations that create new chain termination codons and result in *COL3A1* haploinsufficiency ("null" mutations) [Schwarze et al 2001, Leistritz et al 2010]. The consequence is synthesis of about one half the amount of normal type III procollagen. (See Database of Human Type I and Type III Collagen Mutations.)

In the analysis to date of the mutations identified in *COL3A1*, at least two classes of mutations — substitutions of glycine in the triple helical domain by alanine and introduction of premature termination codons — are underrepresented (in terms of the predicted frequency) among individuals with clinical features of EDS type IV. Thus, some mutations in *COL3A1* may not produce an EDS, vascular type phenotype. It is unclear if individuals with these classes of mutations have limited phenotypes and present at later ages or if there is a molecular explanation for the absence of certain mutation types.

Normal gene product. *COL3A1* encodes the proα1(III) chain of type III procollagen, a major structural component of skin, blood vessels, and hollow organs. The type III procollagen molecule is a homotrimer, with constituent chains 1,466 amino acids in length.

Abnormal gene product. Mutations of *COL3A1* typically result in a structural alteration of type III collagen that leads to intracellular storage and impaired secretion of collagen chains.

References

Published Guidelines/Consensus Statements

1. American Society of Human Genetics and American College of Medical Genetics. Points to consider: ethical, legal, and psychosocial implications of genetic testing in children and adolescents. Available online. 1995. Accessed 7-12-12.
2. National Society of Genetic Counselors. Position statement on genetic testing of minors for adult-onset disorders. Available online. 2012. Accessed 7-12-12.

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Chapter Notes

Author Notes

Web: www.pathology.washington.edu/clinical/collagen

Revision History

- 3 May 2011 (me) Comprehensive update posted live
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