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Vascular Ehlers-Danlos Syndrome

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

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Summary

Clinical characteristics

Vascular Ehlers-Danlos syndrome (vEDS) is characterized by arterial, intestinal, and/or uterine fragility; thin, translucent skin; easy bruising; characteristic facial appearance (thin vermilion of the lips, micrognathia, narrow nose, prominent eyes); and an aged appearance to the extremities, particularly the hands. Vascular dissection or rupture, gastrointestinal perforation, or organ rupture are the presenting signs in most adults with vEDS. Arterial rupture may be preceded by aneurysm, arteriovenous fistulae, or dissection but also may occur spontaneously. The majority (60%) of individuals with vEDS who are diagnosed before age 18 years are identified because of a positive family history. Neonates may present with clubfoot, hip dislocation, limb deficiency, and/or amniotic bands. Approximately half of children tested for vEDS in the absence of a positive family history present with a major complication at an average age of 11 years. Four minor diagnostic features – distal joint hypermobility, easy bruising, thin skin, and clubfeet – are most often present in those children ascertained without a major complication.

Diagnosis/testing

The diagnosis of vEDS is established in a proband by identification of a heterozygous pathogenic variant in *COL3A1*, or, when molecular genetic testing does not identify a *COL3A1* pathogenic variant, on biochemical analysis of type III procollagen from cultured fibroblasts.

Management

Treatment of manifestations: Affected individuals are instructed to seek immediate medical attention for sudden, unexplained pain. Treatment may include medical or surgical management for arterial complications, bowel rupture, or uterine rupture during pregnancy.

Surveillance: May include periodic arterial screening by ultrasound examination, magnetic resonance angiogram, or computed tomography angiogram with and without venous contrast. Blood pressure monitoring on a regular basis is recommended to allow for early treatment if hypertension develops.

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Agents/circumstances to avoid: Trauma (collision sports, heavy lifting, and weight training with extreme lifting); arteriography should be discouraged and used only to identify life-threatening sources of bleeding prior to surgical intervention because of the risk of vascular injury; routine colonoscopy in the absence of concerning symptoms or a strong family history of colon cancer; elective surgery unless the benefit is expected to be substantial.

Evaluation of relatives at risk: The genetic status of at-risk relatives should be clarified through molecular genetic testing or clinical evaluation if the pathogenic variant is unknown.

Pregnancy management: Affected women have a 5% mortality risk with each pregnancy. The issue of management and recommendations is complicated by the recognition that many of the women who became pregnant, and their providers, learn of the diagnosis at the time of delivery and the onset of complications. When the mother's diagnosis is known, maternal risks should be discussed and she should be followed in a high-risk obstetric program.

Other: Affected individuals should carry documentation of their genetic diagnosis, such as a MedicAlert®, emergency letter, or vEDS "passport."

Genetic counseling

Vascular EDS is almost always inherited in an autosomal dominant manner, but rare examples of biallelic inheritance have been reported. About 50% of affected individuals have inherited the *COL3A1* pathogenic variant from an affected parent, and about 50% of affected individuals have a *de novo* pathogenic variant. Each child of an affected individual has a 50% chance of inheriting the pathogenic variant and developing the disorder. Prenatal testing for a pregnancy at increased risk and preimplantation genetic testing are possible in families in which the pathogenic variant in *COL3A1* has been identified.

Diagnosis

Suggestive Findings

Vascular Ehlers-Danlos syndrome (vEDS) **should be suspected** in individuals with any **one** of the following major diagnostic criteria or several minor diagnostic criteria, particularly in those younger than age 40 years. Clinical diagnostic criteria established in 2017 [Malfait et al 2017] are useful to guide the approach to genetic testing.

Major diagnostic criteria

- Arterial aneurysms, dissection, or rupture
- Intestinal rupture
- Uterine rupture during pregnancy
- Family history of vEDS

Minor diagnostic criteria

- Thin, translucent skin (especially noticeable on the chest/abdomen)
- Characteristic facial appearance (thin vermilion of the lips, micrognathia, narrow nose, prominent eyes)
- Acrogeria (an aged appearance to the extremities, particularly the hands)
- Carotid-cavernous sinus arteriovenous fistula
- Hypermobility of small joints
- Tendon/muscle rupture
- Early-onset varicose veins
- Pneumothorax/hemopneumothorax

- Easy bruising (spontaneous or with minimal trauma)
- Chronic joint subluxations/dislocations
- Congenital dislocation of the hips
- Talipes equinovarus (clubfoot)

Establishing the Diagnosis

The diagnosis of vEDS **is established** in a proband with either of the following:

- Identification of a heterozygous pathogenic variant in *COL3A1* on molecular genetic testing (See Table 1.)
- Abnormalities in synthesis and mobility of type III collagen chains on biochemical analysis of type III procollagen from cultured fibroblasts when vEDS is suspected but molecular genetic testing does not identify a *COL3A1* pathogenic variant

Note: (1) When the diagnosis is suspected on clinical grounds, molecular diagnostic testing of *COL3A1* is indicated. (2) The presence of clinical phenocopies and variable expression of the vEDS phenotype warrant the molecular diagnostic approach.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (single-gene testing, multigene panel) and **comprehensive genomic testing** (exome sequencing, exome array, genome sequencing) depending on the phenotype.

Gene-targeted testing requires that the clinician determine which gene(s) are likely involved, whereas genomic testing does not. Because the phenotype of vEDS is broad, individuals with the distinctive major criteria findings described in Suggestive Findings are likely to be diagnosed using gene-targeted testing (see Option 1), whereas those with a phenotype indistinguishable from many other inherited connective tissue disorders are more likely to be diagnosed using genomic testing (see Option 2).

Option 1

When the phenotypic and laboratory findings suggest the diagnosis of vEDS, molecular genetic testing approaches can include **single-gene testing** or use of a **multigene panel**:

- **Single-gene testing.** Sequence analysis of *COL3A1* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications.

- **A multigene panel** that includes *COL3A1* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

  For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Option 2

When the phenotype is indistinguishable from many other inherited connective tissue disorders, **comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) is the best option. **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

If **exome sequencing** is not diagnostic, exome array (when clinically available) may be considered to detect (multi)exon deletions or duplications that cannot be detected by sequence analysis.

For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

Table 1. Molecular Genetic Testing Used in Vascular Ehlers-Danlos Syndrome

Gene [1]	Method	Proportion of Probands with a Pathogenic Variant [2] Detectable by Method
COL3A1	Sequence analysis [3]	>95% [4]
	Gene-targeted deletion/duplication analysis [5]	~1% [6]

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Author, personal observation
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. The low frequency of genomic deletions is consistent with the failure to detect a deletion in 155 specimens submitted for *COL3A1* sequence analysis [Pepin et al 2014; Author, personal experience; Collagen Diagnostic Laboratory]. One 3.5-Mb contiguous gene deletion that includes *COL3A1* was identified by MLPA [Meienberg et al 2010].

Biochemical (Protein-Based) Analysis

Biochemical testing for vEDS requires cultured dermal fibroblasts. Proteins synthesized by these cells are biosynthetically labeled with radiolabeled 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. Alterations in mobility may result from substitutions for glycines in the triple helical domain because they lead to slow folding and increased post-translational modification, or as the result of deletions or duplication or splice site alterations. This testing is used now almost exclusively to characterize the outcome of splice site alterations identified by DNA sequence analysis.

Clinical Characteristics

Clinical Description

The most comprehensive descriptions of clinical features and natural history derive from two types of studies: a cross-sectional and retrospective view obtained at the time of diagnostic testing [Pepin et al 2014] and a nearly 15-year-long cohort study from one group in France [Frank et al 2015]. A retrospective review of the health history of more than 1,200 individuals with vascular Ehlers-Danlos syndrome (vEDS) delineated the natural history of the disorder [Pepin et al 2014]. The majority of individuals were ascertained on the basis of a major

complication (70%), at an average age of 30 years. Median survival in the population was 50 years, with a younger median survival in males (by 5 years) than in females, partially due to a higher rate of lethal vascular events in males than females before age 20 years. A similar rate of complications was reported in the French cohort of 215 individuals with vEDS, but a difference in mean survival based on sex was not observed [Frank et al 2015].

Children

The majority (60%) of individuals with vEDS who are diagnosed before age 18 years are identified because of a positive family history [Pepin et al 2014]. (See Evaluation of Relatives at Risk and Genetic Counseling for discussion of genetic testing of at-risk children to facilitate appropriate intervention in the occurrence of a major complication and implementation of risk-reducing behaviors.)

- Approximately 15% of these individuals had experienced a major complication of vEDS by the time of testing.
- Of the 121 children tested in the absence of a positive family history, 65 presented with a major complication at an average age of 11 years.
- Four minor diagnostic features – distal joint hypermobility, easy bruising, thin skin, and clubfeet – were most often present in those ascertained without a major complication.
- At birth, clubfoot (unilateral or bilateral) was noted in 8% of children with vEDS.
- Hip dislocation, limb deficiency, and amniotic bands appeared in approximately 1% of affected infants.
- Death that occurred in the first two decades of life almost always resulted from spontaneous artery rupture or dissection.
    - Artery rupture, 60% of which involved the aorta, was responsible for all deaths in young males.
    - Death before age 20 years was seen in a 3:1 ratio of males:females. This difference was not noted in the French study because ascertainment was restricted to adults.

Adults

Vascular rupture or dissection and gastrointestinal perforation or organ rupture are the presenting signs in 70% of adults with a *COL3A1* pathogenic variant [Rana et al 2011].

- These 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 was 31 years in this reported group.

Cardiovascular. 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 (66%), head and neck (17%), and extremities (17%).
- The clinical presentation depends on the location of the arterial event.
    - Unexplained acute pain warrants immediate medical attention.
    - Chest pain or symptoms of "heart attack" were described in 80% of the 26 individuals with vEDS later identified to have experienced a coronary artery dissection.
- Ruptures of the chordae tendinae or ventricle of the heart are rare cardiovascular complications.
- Venous varicosities also occur.

Gastrointestinal. Perforation of the gastrointestinal (GI) tract occurs in approximately 15% of individuals with identified *COL3A1* pathogenic variants, though seldom in individuals with null variants.

- Most GI perforations occur in the sigmoid colon.
- Ruptures of the small bowel and stomach have been reported, though infrequently.
- Iatrogenic perforation during colonoscopy has also been reported [Rana et al 2011].
- Bowel rupture is rarely lethal (3%) [Pepin et al 2000], with most deaths reported as a result of unexpected hemorrhage or artery rupture during surgical repair.

Surgical intervention for bowel rupture is often necessary and usually lifesaving, although treatment with antibiotics and fluid support has been used successfully [Author, personal observation]. The successful surgical approach to perforation repair in vEDS includes partial colectomy, colostomy and creation of a Hartman pouch, and reversal after several months. Reports of primary repair are few.

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. Recurrent perforation may lead to colonic resection.

Pulmonary. Spontaneous and/or recurrent pneumothoraces may be the first significant presenting feature of vEDS.

- Hemothorax and hemopneumothorax have been reported, often in association with pulmonary blebs, cystic lesions, and hemorrhagic or fibrous nodules.
- Hemoptysis can be severe and recurrent, even life threatening [Hatake et al 2013].
- Pathologic evaluation may demonstrate acute hematoma, fibrous nodules, vascular disruption, intraluminal and interstitial hemosiderosis, and emphysematous changes [Kawabata et al 2010].
- Successful lung transplantation was reported in one individual with severe pulmonary complications of vEDS [García Sáez et al 2014].

Ocular. Keratoconus has been reported in vEDS [Kuming & Joffe 1977].

Carotid cavernous sinus fistulas typically present with sudden-onset ocular symptoms including blurred vision, diplopia, ocular pain, proptosis, and chemosis and almost always requires rapid intervention to save vision. It affects about 10% of individuals with vEDS with a preponderance among females [Adham et al 2018].

Dental complications include periodontal disease and gingival recession. A study by Ferré et al [2012] characterized the gingival phenotype in vEDS as generalized thinness and translucency of the gingiva with increased fragility. Disorders of the temporomandibular joint and defects in dentin formation are also more common in individuals with vEDS.

Other rare complications include rupture of the spleen or liver [Pepin et al 2000, Ng & Muiesan 2005]. Elastosis perforans serpiginosa is a rare but reported skin finding [Ahmadi & Choi 2011, Ferré et al 2012].

Genotype-Phenotype Correlations

More than 600 unique *COL3A1* pathogenic variants have been aggregated into the Ehlers Danlos Syndrome Variant Database with an additional 250 in ClinVar. Approximately 5% of *COL3A1* variants result in haploinsufficiency. Individuals with a *COL3A1* null variant have a 15-year delay in onset of complications, improved life expectancy (close to that of the US population), and significantly fewer obstetric and bowel complications than are seen with other types of *COL3A1* pathogenic variants [Leistritz et al 2011, Pepin et al 2014, Frank et al 2015].

Among the 1,200 individuals with vEDS described by Pepin et al [2014], survival depended in part on the nature of the pathogenic variant. Survival was longest for those with a null variant and shortest for those with a splice donor site variant that resulted in exon skipping or a substitution for a triple helical glycine residue (in the

repeating Gly-Xaa-Yaa triplets) by a large residue. The location of the variant within the triple helix did not have a discernable effect on survival. Similar survival patterns were described in the French cohort of 126 individuals with *COL3A1* pathogenic variants [Frank et al 2015]. These differences in populations are difficult to use to counsel individuals because of significant intra- and interfamilial variability in age of complication and survival for the same pathogenic variant.

Penetrance

In families identified on the basis of clinical complications, penetrance of the vEDS phenotype appears to be close to 100% in adults with a missense or exon-skipping alteration; the age at which the pathogenic variant becomes penetrant may vary. *COL3A1* null variants have significantly reduced penetrance manifested by the absence of minor diagnostic criteria in 51% of individuals with vEDS identified with a pathogenic null alteration [Leistritz et al 2011].

Nomenclature

The following terms for vEDS have been used:

- **Ehlers Danlos syndrome type IV** was introduced by Beighton in his 1979 summary of heterogeneity in Ehlers Danlos syndrome.
- **Status dysvascularis** was introduced by Georg Sack in 1936; the term was never used extensively.
- **Familial acrogeria,** introduced by Heinrich Gottron in 1940, probably included some individuals with vEDS.
- **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.

Prevalence

There are no good estimates of the prevalence of vEDS in any population. About 1,500 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], leading to a minimum prevalence estimate of 1:200,000. The decreased frequency of certain classes of pathogenic variants suggests that the overall prevalence of individuals with pathogenic variants in *COL3A1* (see Molecular Genetics) could approach that of individuals with pathogenic variants in *COL1A1*, which is estimated at close to 1:50,000.

Because many families with vEDS are identified only after a severe complication or death, it is likely that individuals/families with pathogenic variants in *COL3A1* and a mild phenotype do not come to medical attention and thus go undetected. In addition, because of the perceived rarity of the disorder, it is seldom considered and nonvascular complications may not raise diagnostic suspicion of vEDS.

Genetically Related (Allelic) Disorders

Hypermobile Ehlers-Danlos syndrome (EDS type III). A single report of a family with clinical features of EDS type III and a *COL3A1* pathogenic variant typically associated with vEDS (NM_000090.3: c.2410G>A, p.Gly804Ser; Gly637Ser in the triple helical domain) [Narcisi et al 1994] led to the suspicion of a causative relationship between variants in *COL3A1* 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. The same family is cited in a paper by Pope et al [1996] with an indication that there were three generations with hypermobility and no vascular events.

Familial aortic aneurysm. Type III collagen glycine substitutions and *COL3A1* null pathogenic variants are periodically reported in individuals with familial aortic aneurysm [van de Luijtgaarden et al 2015]. In such

publications, the ability to assess whether the vEDS clinical phenotype is present is quite limited. These rare reports notwithstanding, existence of a subset of individuals with a *COL3A1* pathogenic variant giving rise to the phenotype of familial aortic aneurysm in the absence of other findings of vEDS seems unlikely [Author, personal observation].

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 molecular analysis of *COL3A1*.

Table 2. Disorders to Consider in the Differential Diagnosis of vEDS

DiffDx Disorder	Gene(s)	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/vEDS	Distinguishing from vEDS
Classic EDS	*COL5A1* *COL5A2* [1]	AD	Typically not assoc w/blood vessel, bowel, or organ rupture	• Soft, doughy, stretchy skin • Abnormal scars • Significant large-joint hypermobility
Ehlers-Danlos classic/ vascular type	*COL1A1*	AD	Pathogenic variants in *COL1A1* (all result in substitutions of arginine by cysteine in the triple helical domain) have been reported in persons w/classic EDS & aneurysm & dissection of large vessels [1]	Similar to classic EDS
Kyphoscoliotic EDS (See *FKBP14*-kEDS & *PLOD1*-kEDS.)	*PLOD1* *FKBP14*	AR	Vascular rupture may be a feature	• Progressive scoliosis • Hypotonia • Fragility of the globe
Periodontal Ehlers-Danlos syndrome	*C1R* *C1S*	AD	Bruising & skin staining, particularly shins	• Rare • Features of classic EDS + early periodontal friability, recession, & tooth loss
Isolated arterial aneurysm	See footnote 2.		Single arterial aneurysm or dissection	Usually NOT the result of a type III collagen defect
Loeys-Dietz syndrome	*SMAD2* *SMAD3* *TGFB2* *TGFB3* *TGFBR1* *TGFBR2*	AD	• Vascular findings (cerebral, thoracic, & abdominal arterial aneurysms &/or dissections) • Aggressive arterial aneurysms & high incidence of pregnancy-related complications • Thin translucent skin & easy bruising	• Skeletal manifestations • Craniofacial anomalies • Predisposition to allergic disease
Polycystic kidney disease, autosomal dominant (ADPKD)	*PKD1* *PKD2* [3]	AD	Vascular abnormalities: intracranial aneurysms, aortic root dilatation, & thoracic aorta dissection; mitral valve prolapse	• Generally late onset • Bilateral renal cysts & cysts in other organs • Abdominal wall hernias • Renal manifestations: hypertension, renal pain, & renal insufficiency

Table 2. continued from previous page.

DiffDx Disorder	Gene(s)	MOI	Clinical Features of DiffDx Disorder	
			Overlapping w/vEDS	Distinguishing from vEDS
Marfan syndrome	*FBN1*	AD	Consider Marfan syndrome if presenting vascular complication is an aortic aneurysm or dissection.	• vEDS & Marfan syndrome usually can be distinguished relatively easily on physical exam. • Persons w/Marfan syndrome typically have dolichostenomelia & arachnodactyly, lens dislocation, & dilatation or aneurysm of only the aorta.

AD = autosomal dominant; AR = autosomal recessive; DiffDx = differential diagnosis; EDS = Ehlers-Danlos syndrome; MOI = mode of inheritance

1. A *COL1A1* pathogenic variant p.Arg134Cys was identified in two unrelated children with classic EDS [Nuytinck et al 2000]. The same substitution was subsequently identified in three unrelated persons with aneurysms and rupture of medium-sized arteries in young adulthood. These individuals also had thin and hyperextensible skin, easy bruising, and abnormal wound healing [Malfait et al 2007; Malfait & De Paepe, personal observation]. Pathogenic variants in *COL1A1*, however, are not a major cause of classic EDS [Malfait et al 2005]. See EDS, Classic Type.

2. Familial forms of arterial aneurysm have been linked to at least 16 identified genes (see Heritable Thoracic Aortic Disease Overview).

3. Pathogenic variants *GANAB* and *DNAJB11* may also be associated with ADPKD in rare cases (see ADPKD).

Management

Evaluations Following Initial Diagnosis

There is currently no consensus regarding the appropriate extent of evaluation at the time of initial diagnosis. To establish the extent of disease and needs in an individual diagnosed with vEDS, the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Because of the risk for asymptomatic aneurysm/dissection, initial visualization of the arterial tree is commonly undertaken [Chu et al 2014, Frank et al 2015]; the approach employed varies by geographic region and by institution (see Surveillance). Approach to a vascular evaluation depends on the age of the patient and the circumstances in which the diagnosis is made.
- Because no specific gastrointestinal findings are known to precede or predict bowel rupture, invasive GI evaluation is of no benefit.
- Consultation with a clinical geneticist and/or genetic counselor is recommended.
- Following diagnosis, the most crucial aspect of management is the creation of an organized care team. See Treatment of Manifestations.
- Review lifestyle with the affected individual and emphasize the importance of minimizing collision activities and sports.

Treatment of Manifestations

The most crucial aspect of management is the creation of an organized care team that includes a primary care physician, vascular surgeon, and general surgeon; a geneticist may aid in integration of care. This team is responsible for the organization of ordinary and extraordinary care. In addition, individuals with vEDS should carry documentation of their genetic diagnosis, such as a MedicAlert®, emergency letter, or vEDS "passport."

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

Surgical intervention may be lifesaving 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 addition, an approach of "judicious underhydration" may help to prevent the recognized cycle of complications.
- In general, surgical procedures are more likely to be successful when the treating physician is aware of the diagnosis of vEDS and its associated tissue fragility [Shalhub et al 2014].

There are no guidelines to direct recommendations for elective repair in individuals with aneurysm(s) and vEDS.

- A decision about the timing and approach of an elective vascular procedure or the use of endovascular approaches is typically based on an individualized risk/benefit assessment.
- Reports of successful endovascular approaches are growing but no studies have compared outcomes with endovascular vs open repair.

Prompt surgical intervention of bowel rupture is usually 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 or total colectomy to reduce the risk of recurrent bowel rupture [Frank et al 2015].

  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].

Surveillance

The use of surveillance of the arterial vasculature 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 option, the benefit of surveillance could not be established. As endovascular approaches to management of aneurysms and dissection become more available, earlier intervention is considered and surveillance is seen to have greater benefit. There are, however, no published data assessing the efficacy of screening strategies in identifying 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, noninvasive imaging such as ultrasound examination, magnetic resonance angiogram, or computed tomography angiogram with and without venous contrast is preferred to identify aneurysms, dissections, and vascular ruptures [Chu et al 2014]. Because arterial tear/dissection may result at the site of entry of the catheter and at sites of high-pressure injection, conventional arteriograms are not recommended. When surveillance is undertaken, repeat measure depends on the pathology identified, but in the presence of a normal vascular tree, screening at 18-month intervals appears to be the usual practice.

Blood pressure monitoring on a regular basis is recommended to allow for early treatment if hypertension develops, thus reducing the risk for vascular stress and injury.

Agents/Circumstances to Avoid

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

Arteriography. 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.

Routine colonoscopy. There are several reports of colonoscopy-associated bowel perforation in individuals with vEDS. Virtual colonoscopy, which also involves insufflation, may have similar complications. Routine colonoscopy for cancer screening is discouraged in the absence of concerning symptoms or a strong family history of colorectal cancer. Individuals with vEDS who have a family history of colon cancer are encouraged to use genetic testing for colon cancer risk assessment (provided the genetic etiology of colon cancer has been established in an affected family member). Use of capsular cameras may provide sufficient data in at-risk individuals.

Elective surgery. Because tissue fragility results in a higher risk of surgical complications, elective surgery for individuals with vEDS is generally discouraged unless the benefit is expected to be substantial. In general, avoidance of surgery in favor of more conservative management is advised, although data about elective surgery are just beginning to emerge and this approach needs to be reevaluated.

Evaluation of Relatives at Risk

It is appropriate to evaluate apparently asymptomatic older and younger at-risk relatives of an affected individual to identify as early as possible those who could benefit from surveillance, awareness of treatment for potential complications, and appropriate restriction of high-risk physical activities. Evaluations can include:

- Molecular genetic testing if the pathogenic variant in the family is known;
- Clinical evaluation if the pathogenic variant in the family is not known.

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

Pregnancy Management

Pregnancy has often been actively discouraged for women with vEDS because of high reported risks of mortality. The most extensive study, which included evaluation of more than 500 pregnancies in 253 women [Murray et al 2014], found a mortality rate of about 5% per pregnancy. This is lower than previously identified and may be because a significant number of the women included knew about the diagnosis before pregnancy or delivery. The issue of management and recommendations is complicated by the recognition that many of the women who became pregnant, and their providers, learned of the diagnosis at the time of delivery and the onset of complications.

About half the women in the study had no complications. For others, prematurity, and uterine, cervical, and vaginal tears led to morbidity.

Increasingly, the practice is to plan delivery by cesarean section at 36-38 weeks to try to avoid the extensive tissue injury that can accompany vaginal delivery. This procedure can be associated with an increased risk of hemorrhage and inadvertent damage to nearby abdominal organs.

When the diagnosis is known in the mother, the maternal risks should be discussed and all options considered. The decision to proceed with pregnancy should involve enlarging the care team to include a high-risk obstetric service. Plans for early delivery should include the presence of the vascular surgeon and potentially the general surgeon.

It is essential to educate the pregnant woman regarding possible complications and the need for close monitoring.

Therapies Under Investigation

A clinical trial in France to determine if addition of an angiotensin receptor blocker to celiprolol decreases arterial complications and extends life expectancy is currently underway.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe 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.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of 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; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

Vascular Ehlers-Danlos syndrome (vEDS) is almost always inherited in an autosomal dominant manner. There are rare reports of individuals with biallelic pathogenic variants in *COL3A1* [Jørgensen et al 2015].

Risk to Family Members

Parents of a proband

- About 50% of individuals diagnosed with vEDS have an affected parent.
- A proband with vEDS may have the disorder as the result of a *de novo COL3A1* pathogenic variant. The proportion of affected individuals with a *de novo* pathogenic variant is about 50%.
- Recommendations for the evaluation of parents of a proband with an apparent *de novo* pathogenic variant include physical examination and molecular genetic testing.
- If the pathogenic variant found in the proband cannot be detected in the leukocyte DNA of either parent, possible explanations include a *de novo* pathogenic variant in the proband or mosaicism in a parent.
    - The estimated rate of parental somatic and germline mosaicism is 2%-5%. To date, parents mosaic for a *COL3A1* pathogenic variant are not known to be symptomatic or to have had complications compatible with the diagnosis of vEDS, though further investigation is needed [Legrand et al 2019].
    - Two families in which there appears to be isolated germline mosaicism have been identified [Byers et al 2003, Palmeri et al 2003].
- The family history of some individuals diagnosed with vEDS may appear to be negative because of failure to recognize the disorder in family members, early death of the parent before the onset of symptoms, or late onset of the disorder in the affected parent. Therefore, an apparently negative family history cannot be confirmed unless appropriate clinical evaluation and/or molecular genetic testing has been performed on the parents of the proband.

Sibs of a proband. The risk to the sibs depends on the clinical/genetic status of the proband's parents:

- If a parent of the proband is affected and/or is known to have the *COL3A1* pathogenic variant identified in the proband, the risk to each sib is 50%.
- If the proband has a known *COL3A1* pathogenic variant that cannot be detected in the leukocyte DNA of either parent, the recurrence risk to the sibs is about 1% because of the possibility of parental germline mosaicism.
- If the parents have not been tested for the *COL3A1* pathogenic variant but are clinically unaffected, sibs of a proband are still presumed to be at increased risk for vEDS because of the possibility of reduced penetrance in a parent or parental germline mosaicism.

Offspring of a proband

- Each child of an individual with vEDS has a 50% chance of inheriting the pathogenic variant and developing complications of the disorder.
- In the rare occurrence in which an individual has biallelic *COL3A1* pathogenic variants, 100% of offspring will inherit one of the variants and may be symptomatic.

Other family members. The risk to other family members depends on the status of the proband's parents: if a parent has the pathogenic variant, his or her family members may be 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* pathogenic variant. When neither parent of a proband with an autosomal dominant condition has the pathogenic variant identified in the proband or clinical evidence of the disorder, the pathogenic variant is likely *de novo*. However, additional explanations including alternate paternity or maternity (e.g., with assisted reproduction) and undisclosed adoption could also be explored.

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic 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 asymptomatic individuals younger than age 18 years

- The benefits of testing individuals younger than age 18 years for vEDS include: (1) elimination of concern for those children who do not have the familial pathogenic variant; (2) awareness of and preparedness for potential complications; and (3) restriction of high-impact sports and high-risk activities for those with the pathogenic variant.
- Although vEDS is often considered an adult-onset condition, 12%-24% of individuals have a major complication by age 20 years [Pepin et al 2014, Frank et al 2015]. Genetic testing of at-risk children has been controversial because of the concern that there is no preventive treatment. However, awareness of the condition is a key component of appropriate intervention in the occurrence of a major complication and for implementation of risk-reducing behaviors. In this context, 87% of children tested before age 18 years had not experienced a major complication and the mean age of testing was eight years. Given the opportunity to consider testing for children at 50% risk of having inherited the pathogenic variant, parents usually did not wait until a complication arose or until the child reached majority for a test to be

performed. Instead, they requested that the test be performed to clarify the child's status and allow them to anticipate medical risks [Author, personal communication].

In a family with an established diagnosis of vEDS it is appropriate to consider testing symptomatic individuals regardless of age.

For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the pathogenic variant has been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for vEDS are possible. Given the efficiency of molecular genetic testing and the recognition that essentially all individuals with a biochemical diagnosis of vEDS also have a known *COL3A1* pathogenic variant, molecular genetic testing is the recommended approach for prenatal testing. Experience with use of assisted reproductive technologies for women with vEDS is limited [Bergeron et al 2014].

Biochemical testing. In rare families in which only the biochemical abnormality of type III collagen is known, analysis of cultured CVS cells can be used as an alternative to molecular genetic prenatal testing. Biochemical testing for prenatal diagnosis of vEDS should be performed only if the molecular etiology cannot be 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.

- **Annabelle's Challenge**
  Europa House
  Barcroft Street
  Bury BL9 5BT
  United Kingdom
  Phone: 0161 763 8741; 0800 917 8495
  www.annabelleschallenge.org
- **DEFY Foundation**
  P.O. Box 3386
  West Chester PA 19381
  Email: info@defy-foundation.org
  www.defy-foundation.org
- **Ehlers-Danlos Society - Europe**
  United Kingdom
  Phone: +44 203 887 6132
- **Ehlers-Danlos Support UK**
  United Kingdom
  Phone: 0208 736 5604; 0800 9078518
  www.ehlers-danlos.org
- **The Ehlers-Danlos Society**

Phone: 410-670-7577
www.ehlers-danlos.com

- **MedlinePlus**
  Ehlers-Danlos Syndrome
- **DICE EDS and HSD Global Registry**
  www.ehlers-danlos.com/eds-global-registry

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. Vascular Ehlers-Danlos Syndrome: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
COL3A1	2q32.2	Collagen alpha-1(III) chain	Ehlers-Danlos Syndrome Variant Database COL3A1	COL3A1	COL3A1

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

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

120180	COLLAGEN, TYPE III, ALPHA-1; COL3A1
130050	EHLERS-DANLOS SYNDROME, VASCULAR TYPE; EDSVASC

Gene structure. *COL3A1* comprises 51 exons distributed over 44 kb of genomic DNA (reference sequence NM_000090.3). For a detailed summary of gene and protein information, see Table A, **Gene**.

Note on gene and protein nomenclature. For fibrillar collagen genes of the same clade (*COL1A1*, *COL1A2*, *COL2A1*, *COL3A1*, and *COL5A2*) there is a "legacy" naming system so that all genes have 52 exons – derived from the structure of *COL1A2*. In the case of *COL3A1*, there is fusion of two exons that are equivalent to exons 4 and 5 in *COL1A2* and the fusion exon is called exon 4/5. In addition, there is a second "legacy" protein naming system in which, in addition to the use of the p.Met1 nomenclature, there is a system in which the first glycine of the canonic triple helical domain is referred to as residue 1 in the triple helix. In reports from some laboratories, both systems are used and the difference in protein position between the two systems is indicated. In older reports from some laboratories, the legacy description for protein may be used in combination with the standard description for nucleotide position, leading to considerable confusion.

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

The majority of identified pathogenic variants result in single-amino acid substitutions for glycines in the Gly-X-Y repeat of the triple helical region of the type III procollagen molecule. About a quarter of reported pathogenic variants occur at splice sites, most resulting in exon skipping. A smaller number of splice site variants lead to the use of cryptic splice sites with partial-exon exclusion or intron inclusion. The vast majority of exon-skipping splice site variants 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 variants that create premature termination codons predicted to result in *COL3A1* haploinsufficiency ("null" pathogenic variants) [Schwarze et al 2001, Leistritz et al 2011]. (See Database of Human Type I and Type III Collagen Mutations.)

Of note, at least two classes of *COL3A1* variants are underrepresented (in terms of predicted frequency) among individuals with clinical features of vEDS:

- Substitutions of glycine in the triple helical domain by alanine
- Null variants

Thus, some pathogenic variants in *COL3A1* may not produce a typical vEDS clinical picture. It is unclear if individuals with these classes of pathogenic variants have attenuated or subclinical phenotypes and present at later ages or if there is a molecular explanation for the absence of certain pathogenic variant 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. Pathogenic variants in *COL3A1* typically result in a structural alteration of type III collagen that leads to intracellular storage and impaired secretion of collagen chains. Production of half the normal amount of type III procollagen occurs in a minority of individuals.

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National Society of Genetic Counselors. Position statement on genetic testing of minors for adult-onset conditions. Available online. 2019. Accessed 8-30-21.

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Chapter Notes

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