

Ehlers–Danlos syndrome

Molecular pathology, connective-tissue fragility and phenotype–genotype relationships

Dr Abu Suraih Sakhri

MBBS, MD (Pathology)

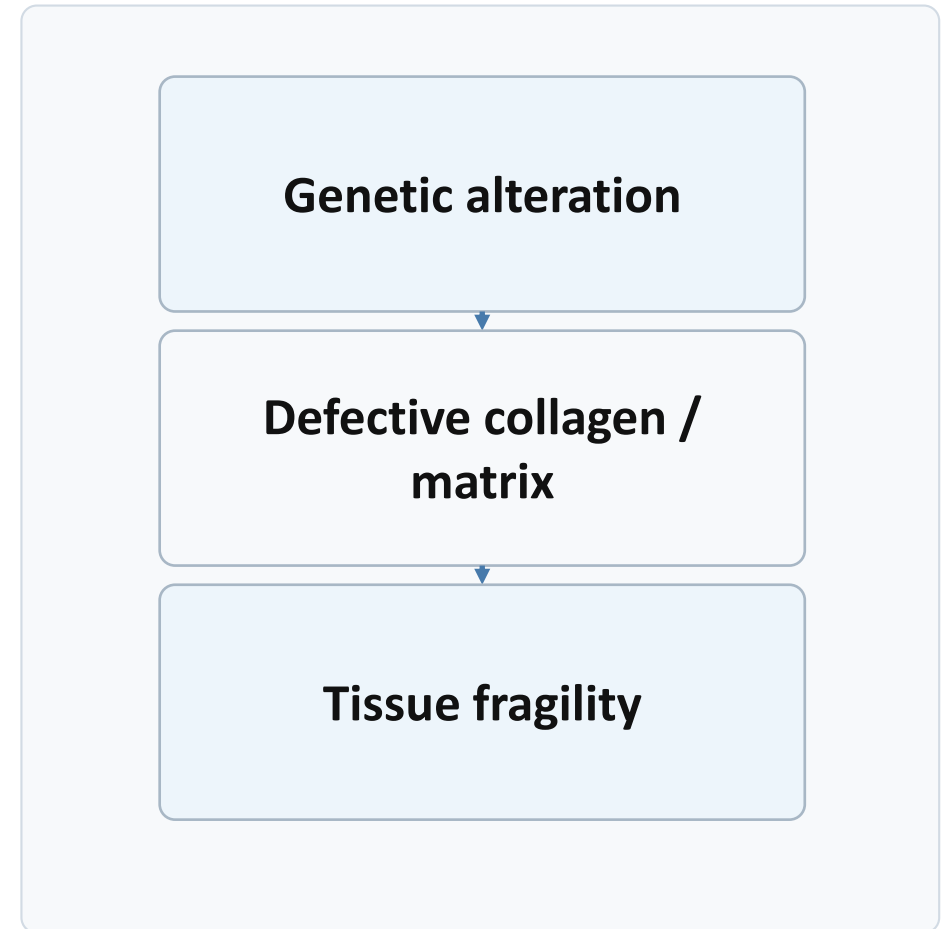
www.abusuraihsakhri.com

Learning objectives

- Trace collagen biosynthesis and identify stages disrupted in EDS.
- Differentiate structural collagen, processing-enzyme and extracellular matrix defects.
- Relate subtype-associated genes to skin, joint and visceral manifestations.
- Explain why vascular EDS requires distinct clinical recognition.

EDS is a group of heritable matrix disorders

- The Ehlers–Danlos syndromes are clinically and genetically heterogeneous.
- Defects affect collagen chains, collagen-processing enzymes or interacting extracellular matrix proteins.
- The unifying consequence is loss of connective-tissue structural integrity.



Why collagen defects produce multisystem disease

- Collagen-rich tissues transmit and withstand mechanical loads.
- A defect in the matrix compromises tensile strength rather than a single organ-specific function.
- The dominant clinical manifestation depends on the collagen or pathway involved.

Skin / wounds

Ligaments / joints

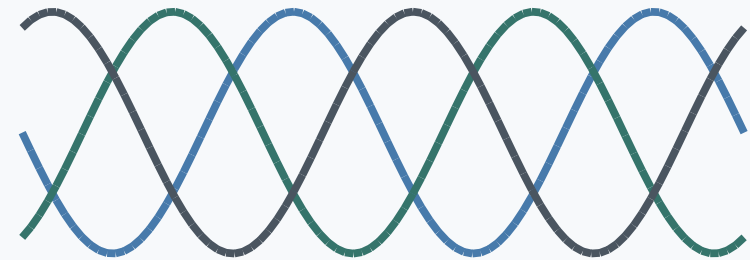
Vessels / viscera

Affected tissues reflect the collagen involved

Tissue	Relevant vulnerability	Clinical expression
Skin	Reduced tensile integrity	Hyperextensibility; Traumatic tears
Joints and ligaments	Reduced passive restraint	Hypermobility; Dislocation
Arteries and bowel	Weak connective-tissue support	Rupture in vascular EDS
Cornea / eye	Ocular tissue fragility	Corneal rupture or retinal detachment in selected EDS forms

Fibrillar collagen has organized molecular architecture

- Collagen α -chains assemble into a triple-helical molecule.
- Some fibrillar collagens are heterotrimers; Type III collagen is a homotrimer.
- Chain identity and processing determine the properties of the mature fibril.



Original triple-helix schematic

Different collagen types implicate different tissues

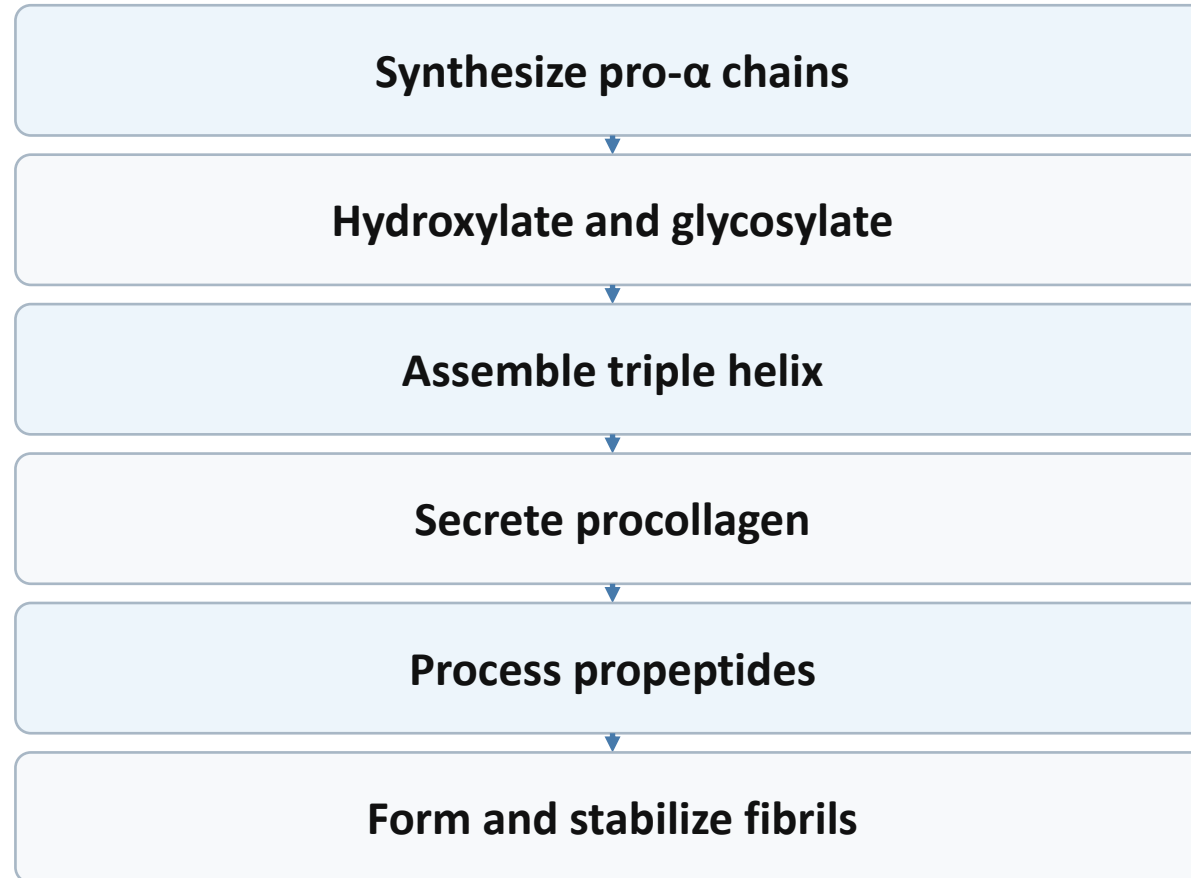
Types I and V

- Important in fibrillar connective-tissue assembly.
- Relevant to classical and arthrochalasia EDS mechanisms.
- Processing and fibril organization are central.

Type III

- Prominent in blood vessels and intestines.
- COL3A1 variants underlie vascular EDS.
- Defects can culminate in spontaneous visceral or arterial rupture.

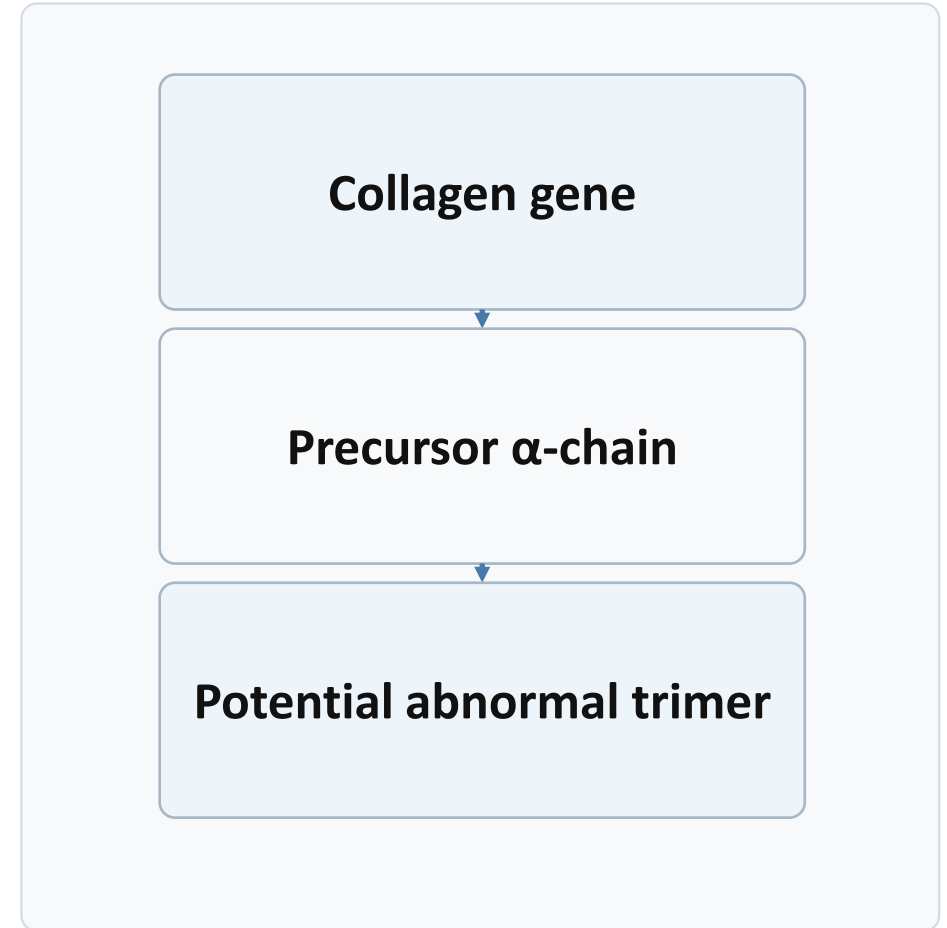
Collagen biosynthesis provides multiple disease targets



An inherited defect at any of several steps can reduce functional collagen strength.

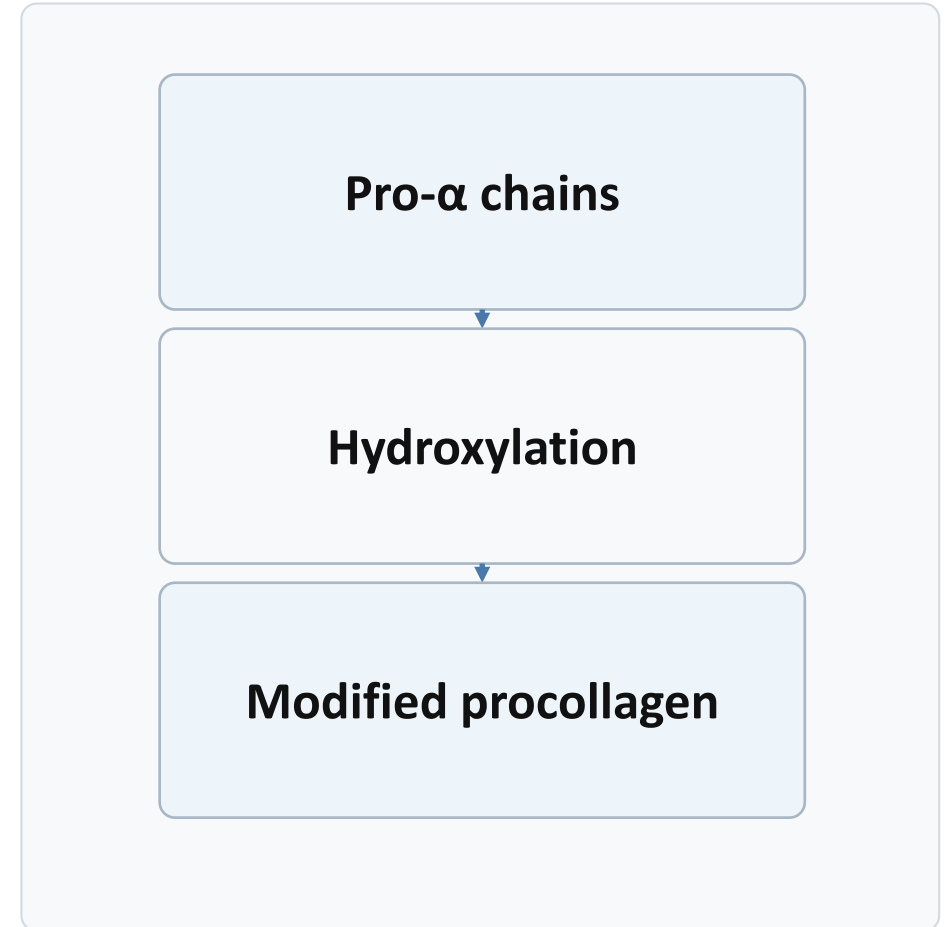
Procollagen precursors require precise chain synthesis

- Collagen chains are translated as precursor pro- α chains.
- Nonhelical propeptides flank the helical region during synthesis.
- Sequence changes can disturb the structure or handling of the assembled molecule.



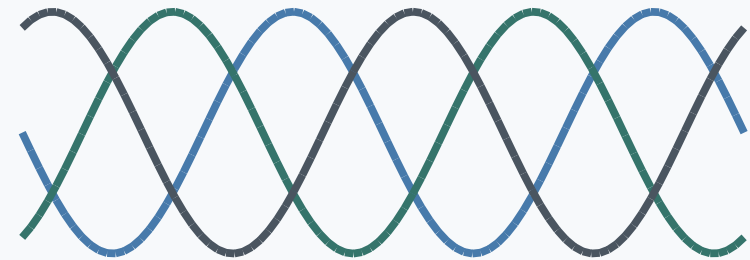
Intracellular hydroxylation prepares collagen

- Proline and lysine residues undergo hydroxylation.
- Lysine can also be glycosylated within the biosynthetic pathway.
- These modifications are part of the pathway that yields structurally stable collagen.



Three chains assemble into a triple helix

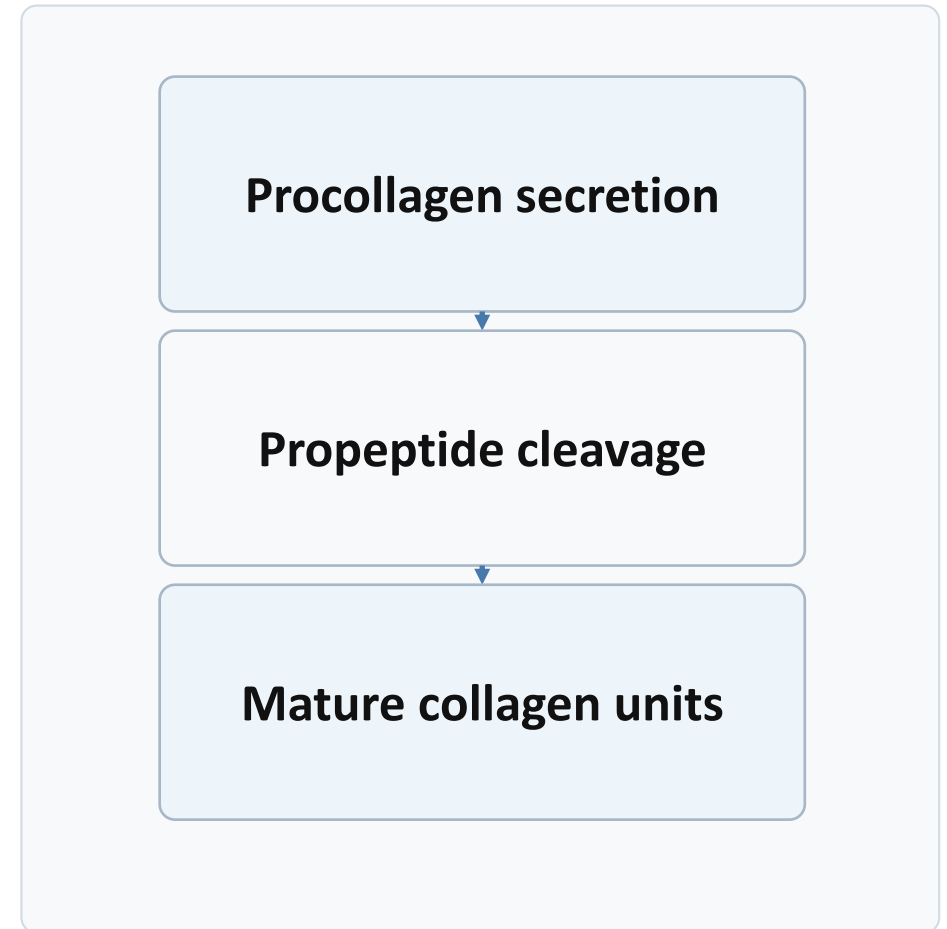
- Appropriate chains align and fold into a collagen triple helix.
- Altered chain structure may interfere with assembly of the multimer.
- This explains severe phenotypes from certain heterozygous structural-gene variants.



Original triple-helix schematic

Secreted procollagen is not yet the mature fibril

- Procollagen leaves the cell with propeptide extensions.
- Endopeptidases process these noncollagenous regions.
- Incorrect cleavage may compromise subsequent fibril organization.



N-terminal processing is a vulnerable step

- N-terminal procollagen cleavage contributes to type I fibrillar collagen maturation.
- Mutations affecting the substrate and mutations affecting the enzyme have different inheritance patterns.
- Arthrochalasia and dermatosparaxis EDS exemplify these defects.

N-propeptide present



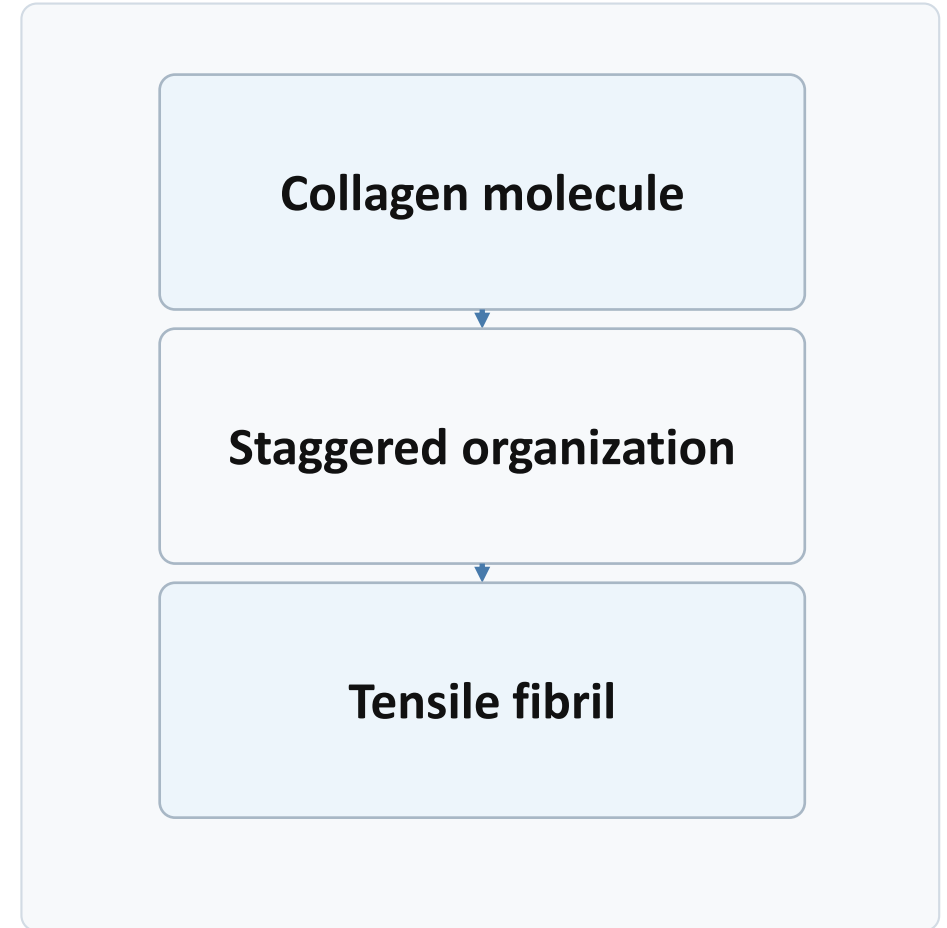
N-propeptide removed



Assembly of mature fibril

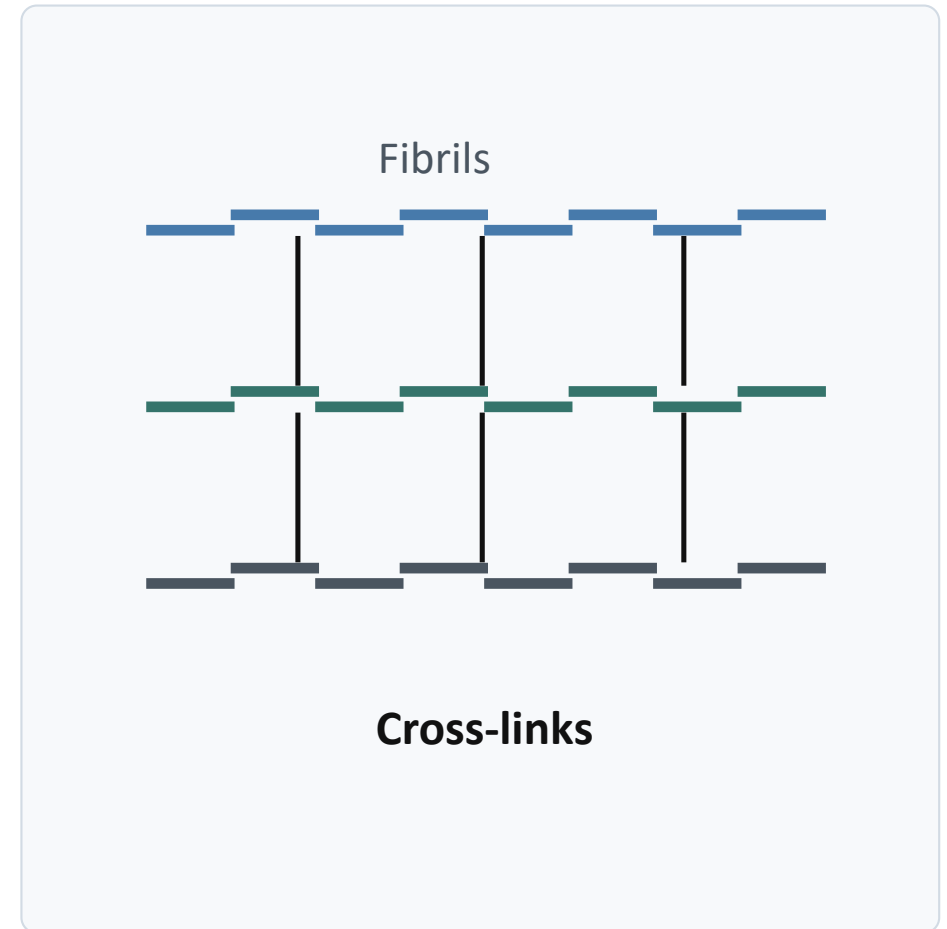
Extracellular assembly generates load-bearing fibrils

- Processed helical molecules polymerize into ordered collagen fibrils.
- Collagen fibrils serve as a tensile framework in connective tissues.
- Impaired collagen assembly is expressed as mechanical weakness under stress.



Cross-linking adds mechanical stability

- Cross-links stabilize collagen after secretion.
- The biosynthetic pathway relies on appropriately modified residues.
- Insufficient molecular stabilization creates structurally weak collagen.

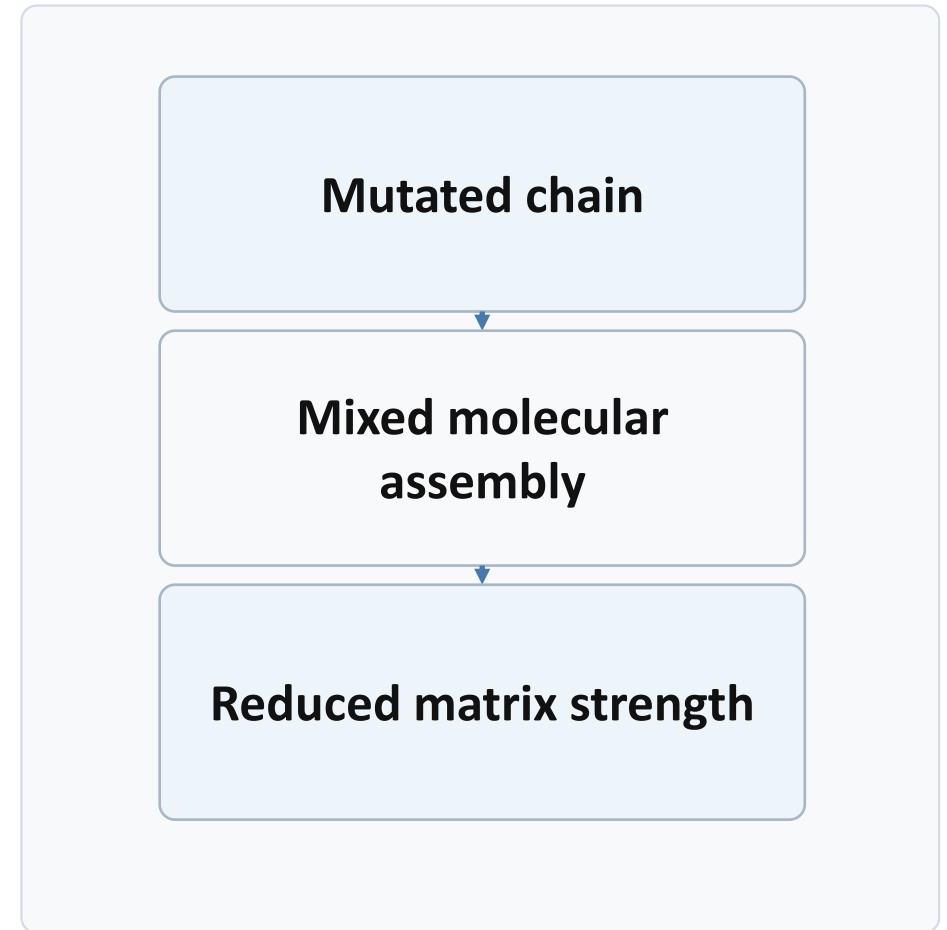


EDS mutations affect three broad functional classes

Molecular class	Illustrative gene(s)	Consequences
Collagen structural proteins	COL3A1, COL5A1, COL1A1, COL1A2	Defective chain structure / quantity
Collagen-modifying or processing enzymes	PLOD1, ADAMTS2	Defective hydroxylation / cleavage
Extracellular matrix-associated proteins	TNXB	Defective matrix organization / assembly

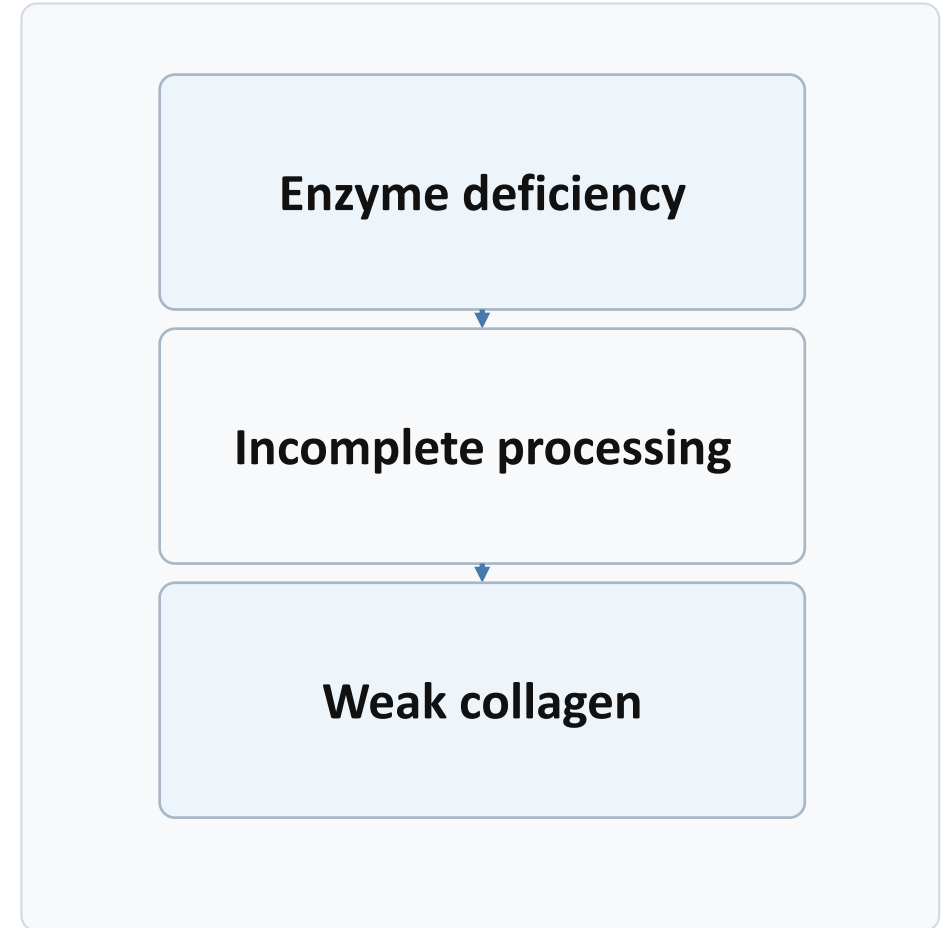
Structural-gene defects compromise collagen assemblies

- Mutant collagen chains can disrupt formation of stable trimers.
- Clinical severity depends on how the particular variant affects the protein.
- Autosomal dominant disease is possible even when one normal allele remains.



Enzyme defects compromise collagen processing

- Enzymes are needed for posttranslational modification and procollagen maturation.
- Loss of a processing enzyme can reduce functional collagen even if collagen genes are intact.
- A recessive inheritance pattern is common when residual enzyme from one allele is sufficient.



Extracellular-matrix defects can resemble collagen defects

- Proteins that bind or organize fibrillar collagen influence matrix architecture.
- Loss of tenascin X can produce a classical-like EDS phenotype.
- Thus a collagenopathy phenotype need not arise from a collagen structural gene.

Matrix-associated protein



Collagen organization



Tissue integrity

Dominant and recessive inheritance coexist in EDS

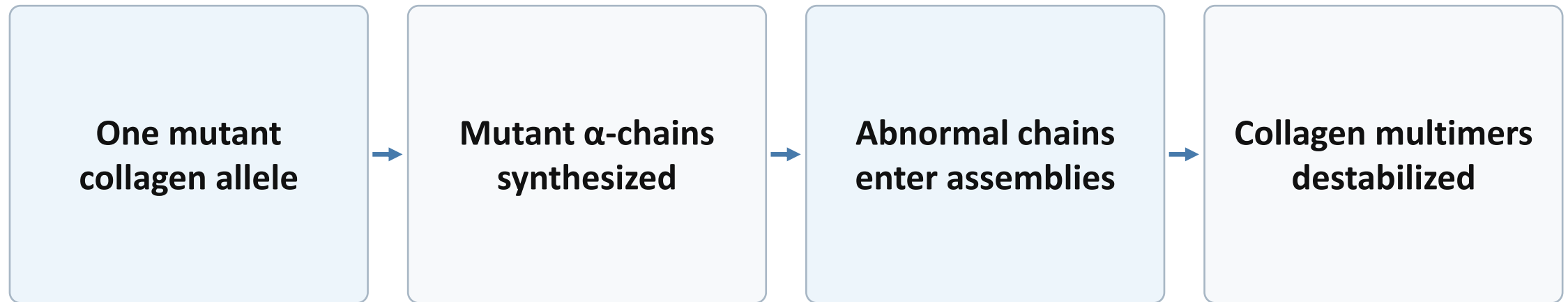
Autosomal dominant

- Can reflect a mutant structural chain interfering with assembly.
- Includes classical, vascular and arthrochalasia EDS classification.
- Affected heterozygotes may express disease.

Autosomal recessive

- Frequently reflects enzyme or matrix-component deficiency.
- Includes dermatosparaxis, classical-like and several rare types.
- Two pathogenic alleles are typically needed.

Dominant-negative effects amplify chain defects



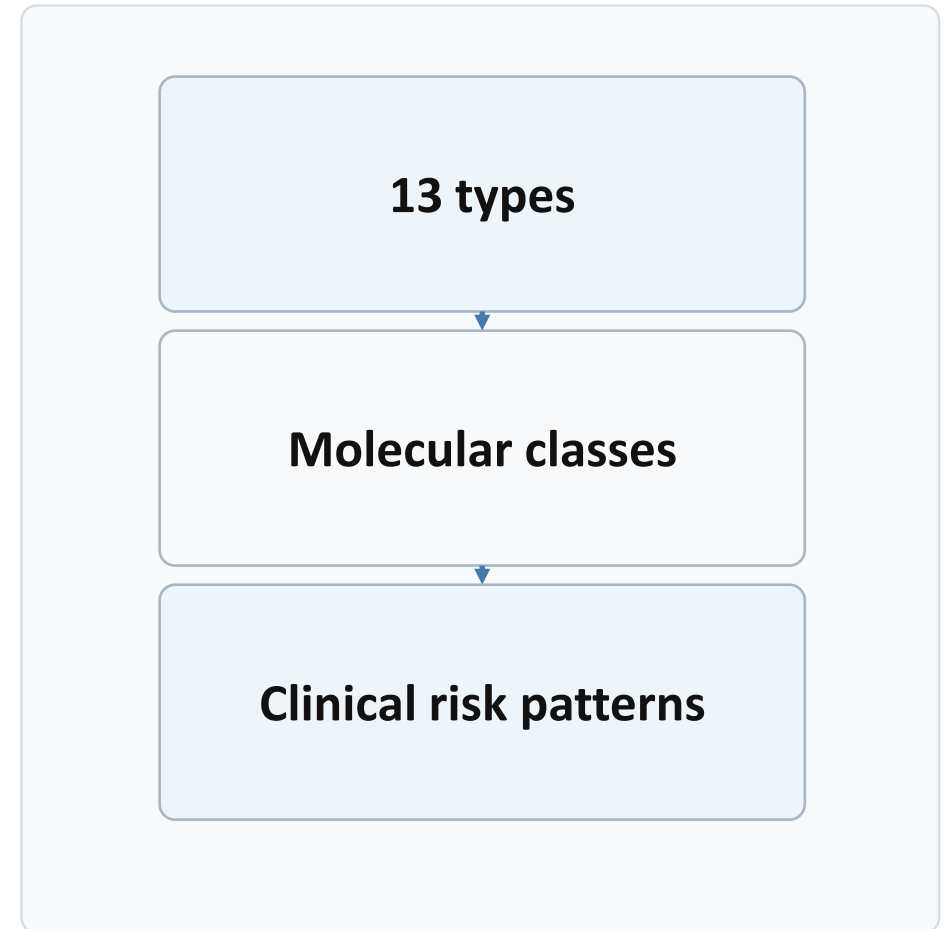
The effect exceeds a simple reduction in the amount of a normal protein.

EDS is phenotypically heterogeneous

- Multiple genes produce overlapping manifestations of skin and joint laxity.
- Different mutations in the same collagen gene can affect synthesis, secretion or molecular structure.
- The same broad syndrome label encompasses very different risks of organ rupture.
- A subtype-oriented assessment is more informative than hypermobility alone.

The textbook uses the 2017 classification of 13 EDS types

- Robbins organizes EDS into 13 subtypes.
- Subtypes differ in involved genes, typical manifestations and inheritance.
- The 2017 scheme is the framework used for this lecture; An updated classification was still in development in 2026.



Autosomal-dominant groups in the 2017 table

Subtype	Gene(s)	Inheritance
Classical	COL5A1; COL1A1 (rare) in Table 5.5	AD
Vascular	COL3A1; COL1A1 (rare)	AD
Hypermobile	No gene established	AD (2017 table)
Arthrochalasia	COL1A1; COL1A2	AD
Periodontal	C1R; C1S	AD
Myopathic	COL12A1	AD or AR

Autosomal-recessive groups in the 2017 table

Subtype	Associated gene(s)	Inheritance
Classical-like	TNXB	AR
Cardiac-valvular	COL1A2	AR
Dermatosparaxis	ADAMTS2	AR
Kyphoscoliotic	PLOD1; FKBP14	AR
Brittle cornea syndrome	ZNF469; PRDM5	AR
Spondylodysplastic	B4GALT7; B3GALT6; SLC39A13	AR
Musculocontractural	CHST14; DSE	AR

The classification is not a severity ranking

- Subtype names identify particular phenotypic or molecular patterns.
- No single finding is sufficient to infer the underlying gene in all cases.
- Subtypes with similar joint findings can differ greatly in vascular and visceral risk.
- Classification guides investigation; A molecular finding must be interpreted with the phenotype.

Classical EDS has prominent cutaneous abnormalities

- Hyperextensible, fragile skin is a prominent manifestation.
- Minor trauma may produce gaping wounds and difficult surgical repair.
- Joint hypermobility and dislocation susceptibility can accompany skin disease.
- The molecular association centers on type V collagen.

Type V collagen defects are central to classical EDS

- The narrative identifies COL5A1 and COL5A2 variants in most classical cases.
- Type V collagen participates in the organization of fibrillar collagen.
- Disordered organization diminishes the tensile integrity of skin and supporting tissues.

Type V collagen defect



**Fibril organization
impaired**



Cutaneous fragility

Classical EDS illustrates mechanical wound failure

- Fragile skin can split under relatively minor force.
- Wound edges may not hold normal tension during repair.
- Surgical closure can be challenging because connective tissue lacks normal strength.

Minor skin injury



Gaping defect

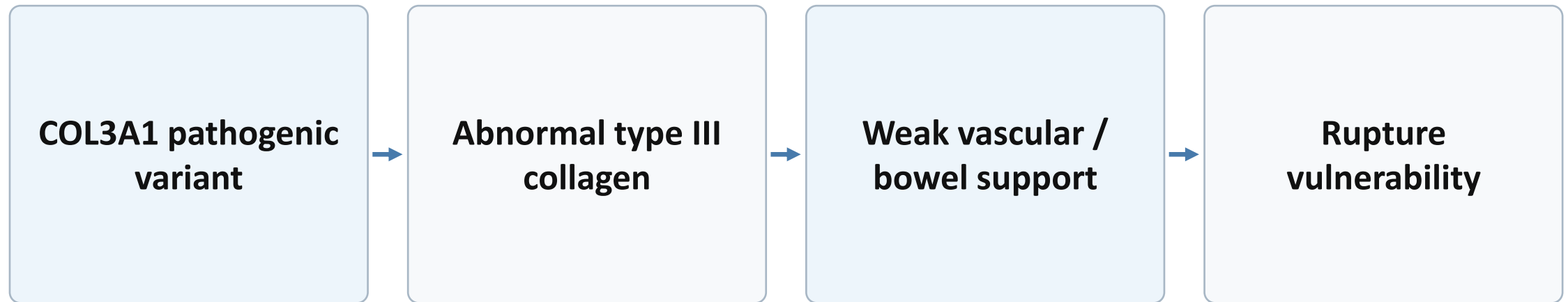


Difficult wound closure

Vascular EDS has a distinct risk profile

- The principal underlying molecule is type III collagen.
- Arterial and intestinal tissues are especially susceptible.
- Spontaneous rupture or dissection can be a major presentation.
- Marked skin hyperextensibility is not generally typical of this subtype.

COL3A1 abnormalities produce vascular EDS



Type III collagen is especially important in blood vessels and intestines.

Vascular EDS can involve deficient chain synthesis

- Some COL3A1 variants reduce production of pro- α 1(III) chains.
- Fewer normal chains may be available for collagen assembly.
- This is one of several molecular paths toward vascular fragility.

Variant alters production



Less pro- α 1(III)



Weak tissue support

Vascular EDS can involve secretion defects

- Some COL3A1 variants interfere with secretion of type III procollagen.
- Intracellular chain synthesis need not equate to normal extracellular matrix content.
- The result may still be loss of tensile strength at the organ level.

Procollagen produced



Secretion impaired



Matrix collagen reduced

Vascular EDS can involve abnormal collagen structure

- Other COL3A1 variants produce structurally abnormal type III collagen.
- Abnormal chains may adversely affect assemblies formed with normal chains.
- Dominant-negative behavior can contribute to severe disease in heterozygotes.

Abnormal type III chain



Trimer destabilization



Organ fragility

Type III collagen explains target-organ vulnerability

Arterial wall

- Connective tissue resists intraluminal mechanical force.
- Impaired type III collagen weakens the structural framework.
- Arterial dissection or rupture may occur.

Intestinal wall

- Collagen reinforces tissue under distension.
- Reduced tensile integrity predisposes to bowel wall failure.
- Spontaneous intestinal rupture is a major hazard.

Do not exclude vascular EDS for lack of stretchy skin

- The vascular phenotype differs from the archetypal hyperextensible skin presentation.
- Major-organ fragility may dominate the clinical picture.
- A relevant history of arterial or intestinal rupture deserves subtype-directed investigation.
- Connective-tissue syndromes cannot be safely triaged by a single sign.

Hypermobile EDS illustrates incomplete gene discovery

- Hypermobile EDS is one of the 13 types in the 2017 framework.
- Its disease gene as unknown.
- Clinical hypermobility does not by itself identify the molecular mechanism.
- Avoid assigning a particular collagen-gene mutation to hypermobile EDS without evidence.

Joint hypermobility is a phenotype, not a genotype

What examination can establish

- The range of motion exceeds the usual physiological range.
- Joint instability or dislocations may coexist.
- Other tissue findings help narrow the differential.

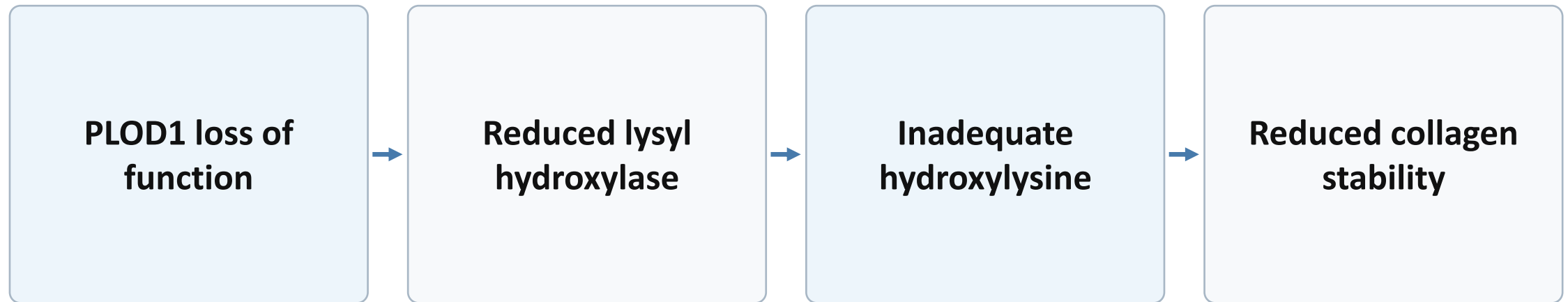
What it cannot establish alone

- A specific EDS subtype.
- A COL3A1 or COL5A1 pathogenic variant.
- The presence or absence of life-threatening vascular fragility.

Kyphoscoliotic EDS highlights hydroxylation defects

- PLOD1 as a key cause of kyphoscoliotic EDS.
- PLOD1 encodes lysyl hydroxylase.
- The deficit interferes with collagen stabilization.
- The 2017 classification also lists FKBP14-associated kyphoscoliotic EDS.

PLOD1 deficiency impairs lysine hydroxylation



This is an enzyme-deficiency mechanism with autosomal-recessive inheritance.

Hydroxylysine is needed for stable collagen

- Lysine hydroxylation prepares collagen for normal stabilization.
- A severe lysyl hydroxylase deficit can compromise both intra- and intermolecular strength.
- This is mechanistically different from a defect in a collagen structural chain.

Lysine modification



Stabilizing interactions



Tissue strength

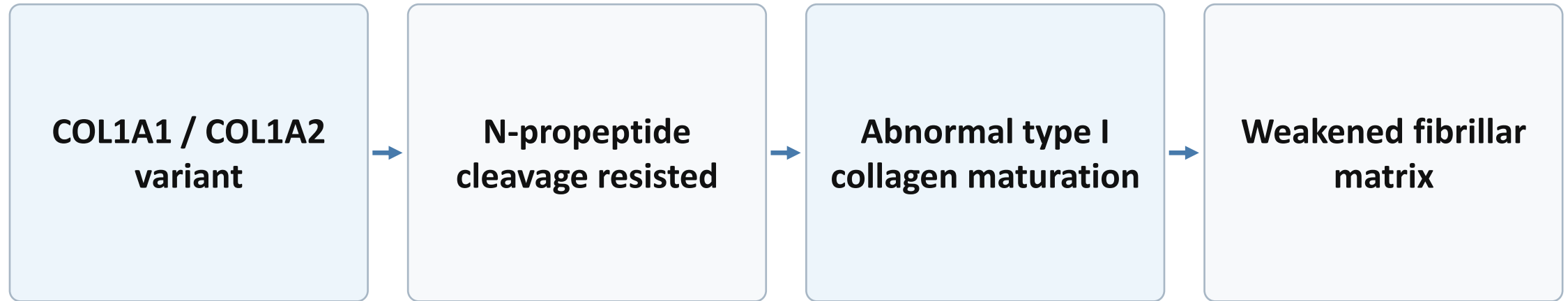
Kyphoscoliotic EDS can endanger ocular integrity

- The EDS section associates kyphoscoliotic forms with ocular fragility.
- Corneal rupture and retinal detachment are important potential complications.
- This demonstrates that not all EDS complications are confined to skin and joints.
- An ocular phenotype may direct attention toward a specific subtype.

Arthrochalasia EDS is a substrate-processing defect

- Autosomal-dominant arthrochalasia EDS is linked to COL1A1 and COL1A2.
- Affected procollagen chains can resist N-terminal propeptide cleavage.
- A structurally abnormal substrate is produced despite the presence of processing enzymes.
- This disrupts the transition from procollagen to mature collagen.

Failure of propeptide removal disrupts fibrils



The mutation is in the substrate protein, not necessarily the enzyme.

Dermatosparaxis EDS is a processing-enzyme defect

- Autosomal-recessive dermatosparaxis EDS is linked to ADAMTS2.
- ADAMTS2 encodes the procollagen N-peptidase required for collagen processing.
- An enzyme defect blocks normal cleavage of procollagen.
- Its inheritance differs from arthrochalasia despite a shared biochemical step.

Same biochemical step, different molecular lesions

Arthrochalasia EDS

- Collagen substrate is abnormal.
- COL1A1 or COL1A2.
- Resistant to N-terminal cleavage.
- Autosomal dominant.

Dermatosparaxis EDS

- Processing enzyme is deficient.
- ADAMTS2.
- N-peptidase activity is defective.
- Autosomal recessive.

Classical-like EDS involves tenascin X

- Classical-like EDS is associated with TNXB variants.
- TNXB encodes tenascin X, an extracellular matrix glycoprotein.
- Tenascin X interacts with fibrillar collagens I, III and V.
- Loss of a collagen-associated protein can mimic a collagen structural disorder.

Tenascin X links collagen to matrix organization

- Collagen molecules operate within a wider extracellular matrix network.
- Tenascin X participates in interactions with fibrillar collagen.
- Matrix disorganization is another route to connective-tissue laxity.

Tenascin X abnormal



**Collagen association
altered**



**Matrix mechanical
weakness**

Other 2017 subtypes extend the molecular spectrum

Subtype	Gene(s) listed	Genetic pattern
Periodontal	C1R, C1S	AD
Myopathic	COL12A1	AD / AR
Cardiac-valvular	COL1A2	AR
Brittle cornea	ZNF469, PRDM5	AR

Rare subtypes implicate additional matrix pathways

Subtype	Genes	Inheritance
Spondylodysplastic	B4GALT7; B3GALT6; SLC39A13	AR
Musculocontractural	CHST14; DSE	AR
Classical-like	TNXB	AR
Kyphoscoliotic	PLOD1; FKBP14	AR

Skin hyperextensibility reflects reduced resistance

- Skin can be stretched beyond the usual range when its collagen framework is weak.
- The sign represents altered material properties of the connective tissue.
- Its prominence varies by subtype and should not be used as a universal criterion.

Weak dermal collagen



Mechanical traction



Excess extension

Easy bruising and skin fragility are related findings

- Fragile connective-tissue support is vulnerable to minor trauma.
- Visible bruising and skin tears can occur disproportionately to injury.
- Severity and combination of cutaneous findings vary across EDS types.

Fragile supporting matrix



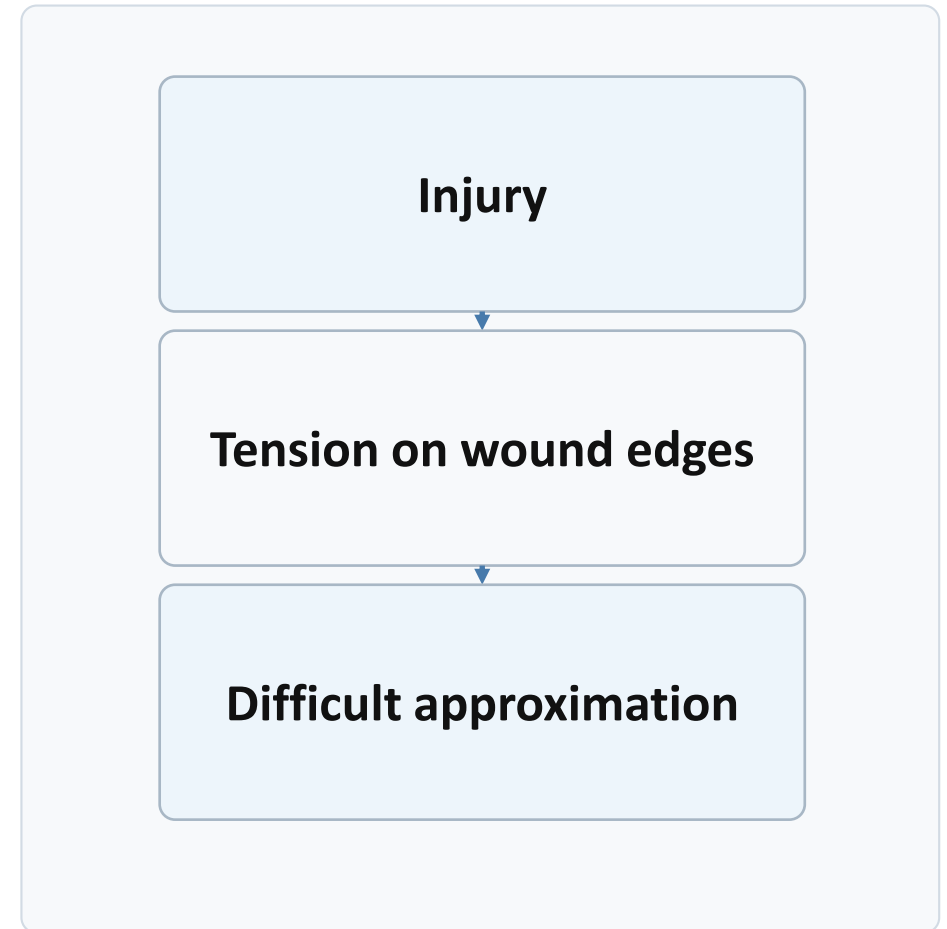
Minor force



Bruise / skin injury

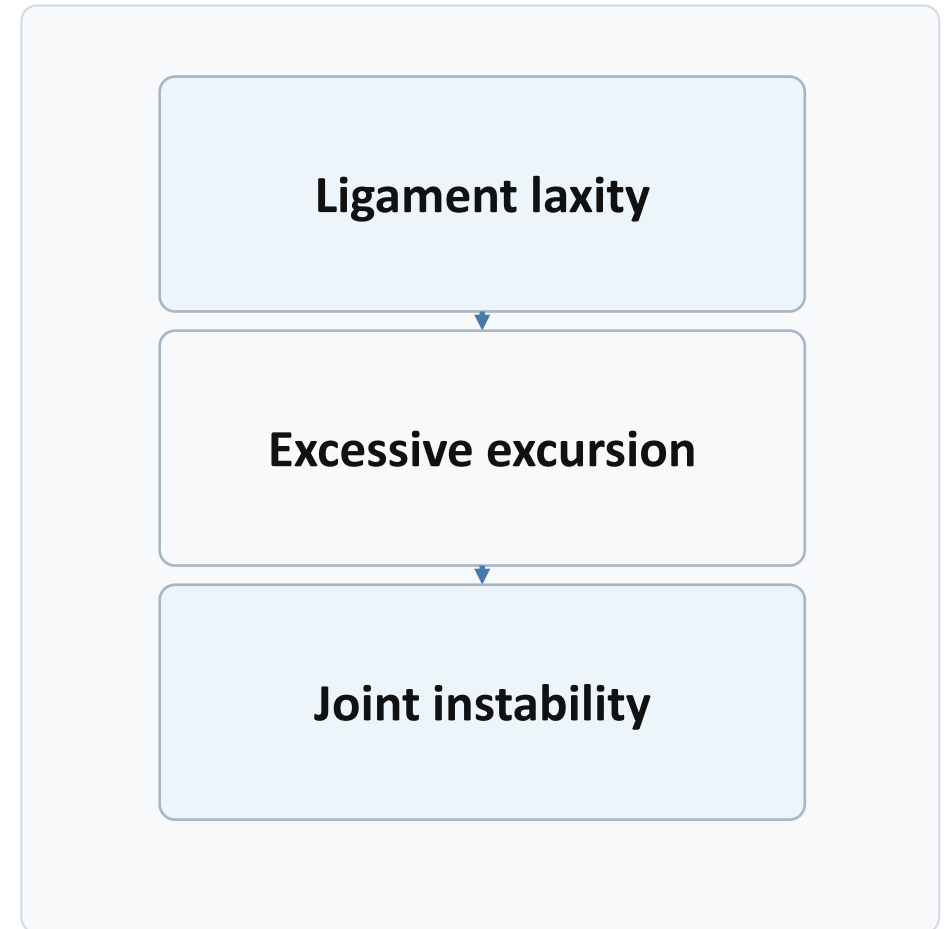
Poor wound repair is a direct clinical consequence

- Tissue apposition requires collagen that can withstand tension.
- In EDS, inadequate tensile strength can cause gaping or difficult-to-repair wounds.
- The clinical problem is structural support during healing, not simply slow cell proliferation.



Joint hypermobility reflects reduced passive stability

- Ligaments and connective tissues normally limit joint range.
- Weak connective-tissue support permits excessive motion.
- Instability predisposes to recurrent subluxation or dislocation.



Dislocation risk links anatomy to functional effects

- Abnormal joint range does not necessarily imply functional benefit.
- Loss of passive mechanical restraint increases susceptibility to instability.
- Repeated dislocations can become a dominant clinical complaint.
- Joint findings should be interpreted together with skin and systemic manifestations.

Visceral rupture is a subtype-specific red flag

Vascular EDS

- Large artery rupture or dissection.
- Colon rupture.
- Type III collagen / COL3A1.

Selected nonvascular subtypes

- Kyphoscoliotic: Ocular fragility.
- Classical: Diaphragmatic hernia reported.
- These patterns differ from arterial/intestinal rupture.

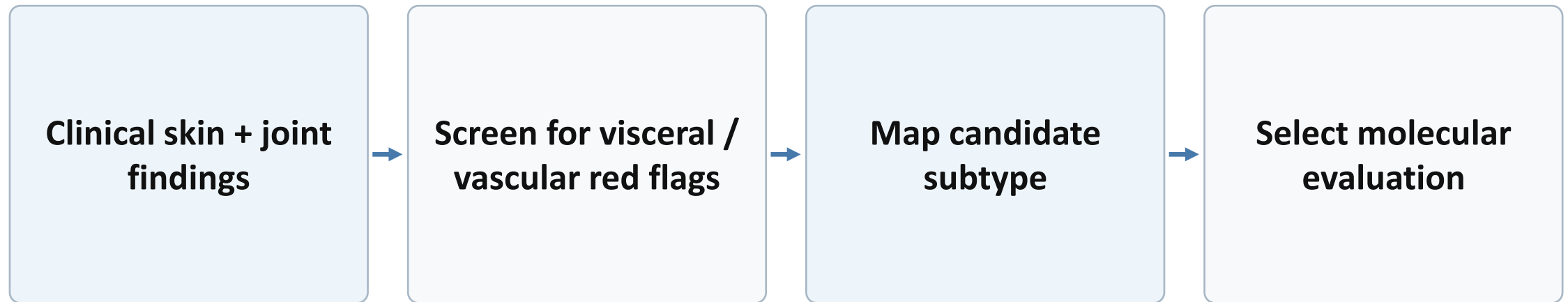
Clinical assessment must look beyond hypermobility

- Characterize skin stretchability, fragility, bruising and wound history.
- Ask about recurrent joint dislocations and family history.
- Identify arterial, bowel or ocular complications suggesting higher-risk forms.
- Use the combined phenotype to select appropriate confirmatory evaluation.

Genotype, mechanism and organ risk must be integrated

Example	Primary mechanism	Distinguishing consequence
Classical EDS	Type V collagen abnormalities	Skin / wound fragility
Vascular EDS	Type III collagen abnormalities	Arterial / bowel rupture
Kyphoscoliotic EDS	Lysyl hydroxylase deficit	Reduced collagen stability; Ocular risk
Arthrochalasia EDS	Type I procollagen processing resistance	Defective collagen maturation
Dermatosparaxis EDS	Procollagen N-peptidase deficiency	Defective collagen maturation

A phenotype-first diagnostic pathway avoids overcalling



A clinical pattern raises suspicion; Subtype confirmation depends on the relevant evidence.

Vascular EDS merits molecular confirmation

- GeneReviews identifies pathogenic or likely pathogenic COL3A1 variants as establishing vascular EDS.
- Arterial, intestinal or family-history clues warrant targeted suspicion.
- A variant of uncertain significance alone does not confirm or exclude the diagnosis.
- Molecular testing should be interpreted in a genetics-informed clinical assessment.

Interpreting negative or ambiguous testing

- A negative result for one gene does not establish an alternative EDS subtype.
- Hypermobile EDS has no established single molecular diagnostic gene in the 2017 framework.
- An uncertain variant is not equivalent to a pathogenic variant.
- Reassess phenotype, test scope and competing disorders when findings conflict.

Marfan syndrome is an important differential

Ehlers–Danlos syndromes

- Core tissue defect involves collagen pathways / matrix proteins.
- Skin fragility and joint hypermobility can dominate.
- Specific EDS forms threaten bowel and arteries.

Marfan syndrome

- Linked to FBN1 / fibrillin.
- Skeletal, ocular and cardiovascular manifestations dominate.
- Aortic root disease is a major concern.

Other collagen-related diseases differ by target tissue

EDS

- Skin, ligaments, joints and selected viscera.
- Collagen structure, maturation or extracellular organization.
- Distinct phenotypes and inheritance patterns.

Other disorders

- Osteogenesis imperfecta: Particularly skeletal fragility.
- Alport syndrome: Collagen-associated renal / auditory disease.
- Epidermolysis bullosa: Skin separation from adhesion defects.

Clinical case: Skin and joint phenotype

CLINICAL PRESENTATION

A patient has markedly stretchable, fragile skin, bruises after minor trauma, and recurrent joint dislocation. Minor cuts produce wide, difficult-to-close wounds.

Which pathophysiologic defect best explains the cutaneous and joint findings?

Deficient tensile integrity of collagen-rich connective tissues. A classical EDS pattern is plausible; Clinical findings alone do not establish a gene.

Clinical case: Suspected vascular EDS

CLINICAL PRESENTATION

A young adult develops a spontaneous arterial complication. Examination shows easy bruising, but the skin is not strikingly hyperextensible.

Does the absence of pronounced skin hyperextensibility argue against all forms of EDS?

No. Vascular EDS can lack marked skin hyperextensibility. COL3A1-associated type III collagen disease should be considered, followed by appropriate genetics assessment.

Clinical case: Two different processing defects

CLINICAL PRESENTATION

Two inherited EDS-like disorders affect collagen N-terminal processing. In one the procollagen substrate resists cleavage; In the other the cleavage enzyme is deficient.

Predict the genes and inheritance categories.

Arthrochalasia: COL1A1/COL1A2, autosomal dominant. Dermatosparaxis: ADAMTS2, autosomal recessive.

Four molecular pathways to tissue fragility

Collagen chain defect → unstable multimer

PLOD1 defect → poor hydroxylation

ADAMTS2 defect → failed cleavage

TNXB defect → matrix disorganization

Different mutations converge on loss of connective-tissue strength.

High-yield distinctions for examination and practice

Question	High-yield distinction
Is EDS one disorder?	No: Clinically and genetically heterogeneous syndrome family.
Why hypermobility and stretchy skin?	Reduced strength of collagen-rich supporting tissues.
What marks vascular EDS?	Type III collagen abnormality and arterial / intestinal fragility.
Why two inheritance patterns?	Structural dominant-negative effects versus recessive loss of enzyme / matrix function.
Is hypermobile EDS gene-known?	No established causative gene in the 2017 scheme.

References and classification scope

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026. Chapter 5, pp 130–131; Table 5.5.
- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026. Chapter 1, Fig. 1.17 (collagen biosynthesis).
- Byers PH. Vascular Ehlers-Danlos Syndrome. GeneReviews. Updated 2025-04-10.
- Ehlers-Danlos Support UK. The types of Ehlers-Danlos syndrome. Reviewed 2026-08-29.

Subtype organization follows the textbook's 2017 classification; changes under development for 2026 are not assumed or retroactively attributed to Robbins.