COLLAGEN METABOLISM

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Amino acids in formation of collagen

Collagen contains specific amino acids – Glycine, Proline, Hydroxyproline. These amino acids have a regular arrangement in each of the three chains of these collagen subunits.

The sequence often follows the pattern Gly-Pro-X or Gly-X-Hyp, where X may be any of various other amino acid residues.

Proline or hydroxyproline constitute about 1/6 of the total sequence.

Glycine (Gly) is found at almost every third residue.

Proline (Pro) makes up about 17% of collagen.

Hydroxyproline is derived from proline and Hydroxylysine derived from lysine. Depending on the type of collagen, varying numbers of hydroxylysines are glycosylated (mostly having disaccharides attached).

Because glycine is the smallest amino acid with no side chain, it plays a unique role in fibrous structural proteins.

Collagen metabolism

Chemistry of collagen

-It is a composed of a triple helix, which generally consists of three chains (α1, α2 and α3) .

Fibers

Once the concentration of tropocollagen is sufficiently high, the molecules will begin to aggregate in a very specific way.

The tropocollagen rods have "sticky ends" that link together to make long strands, and the rods also stack laterally like bundles of wood.

The final result is called a collagen fiber. These fibers make up the collagenous tissues of our bodies.

Regeneration

Like all tissues of the body, collageneous tissues are subject to wear and tear. Unlike some proteins, such as elastin, collagen can be synthesized throughout the body's lifetime.

This is why bones (which are built on a collagen template) can heal naturally even after adulthood.

Breakdown

Collagen degradation is less well-understood than collagen formation. It is, however, known that collagen is relatively resistant to being broken down.

Its tightly packed triple helical structure and fibrous nature offers few weak points for protein-snipping enzymes called collagenases to exploit.

It is much easier for the enzymes to cut denatured collagen, such as that found in injured tissue.

Synthesis of collagen

1- Transcription of mRNA:

There are approximately 34 genes associated with collagen formation, each coding for a specific mRNA sequence.

-The beginning of collagen synthesis begins with turning on genes which are associated with the formation of a particular alpha peptide (typically alpha 1, 2 or 3).

2- Pre-pro-peptide Formation:

Once the final mRNA exits from the cell nucleus and enters into the cytoplasm it links with the ribosomal subunits and the process of translation occurs.

-The early/first part of the new peptide is known as the signal sequence.

-The signal sequence on the N-terminal of the peptide is recognized by a signal recognition particle on the endoplasmic reticulum, which will be responsible for directing the pre-pro-peptide into the endoplasmic reticulum.

-Therefore, once the synthesis of new peptide is finished, it goes directly into the endoplasmic reticulum for post-translational processing.

3- Alpha Peptide to Procollagen:

-Three modifications of the pre-pro-peptide

-1) The signal peptide on the N-terminal is dissolved, and the molecule is now known as *propeptide* (not procollagen).

-2) Hydroxylation of lysines and prolines on propeptide by the enzymes *prolyl hydroxylase* and *lysyl hydroxylase* (to produce hydroxyproline and hydroxylysine) occurs to aid crosslinking of the alpha peptides.

-It is an enzymatic step that requires vitamin C as a cofactor.

-In scurvy, the lack of hydroxylation of prolines and lysines causes a looser triple helix

-3) Glycosylation occurs by adding either glucose or galactose monomers onto the hydroxyl groups that were placed onto lysines, but not on prolines.

-From here the hydroxylated and glycosylated propeptide twists towards the left very tightly and then three propeptides will form a triple helix.

-It is important to remember that this molecule, now known as *procollagen* (not propeptide) is composed of a twisted portion (center) and two loose ends on either end.

-At this point the procollagen is packaged into a transfer vesicle destined for the golgi apparatus.

4- Golgi Apparatus Modification:

-In the golgi apparatus, the procollagen goes through one last post-translational modification before being secreted out of the cell.

-In this step oligosaccharides (not monosaccharides like in step 3) are added, and then the product is packaged into a secretory vesicle destined for the extracellular space.

5- Formation of tropocollagen:

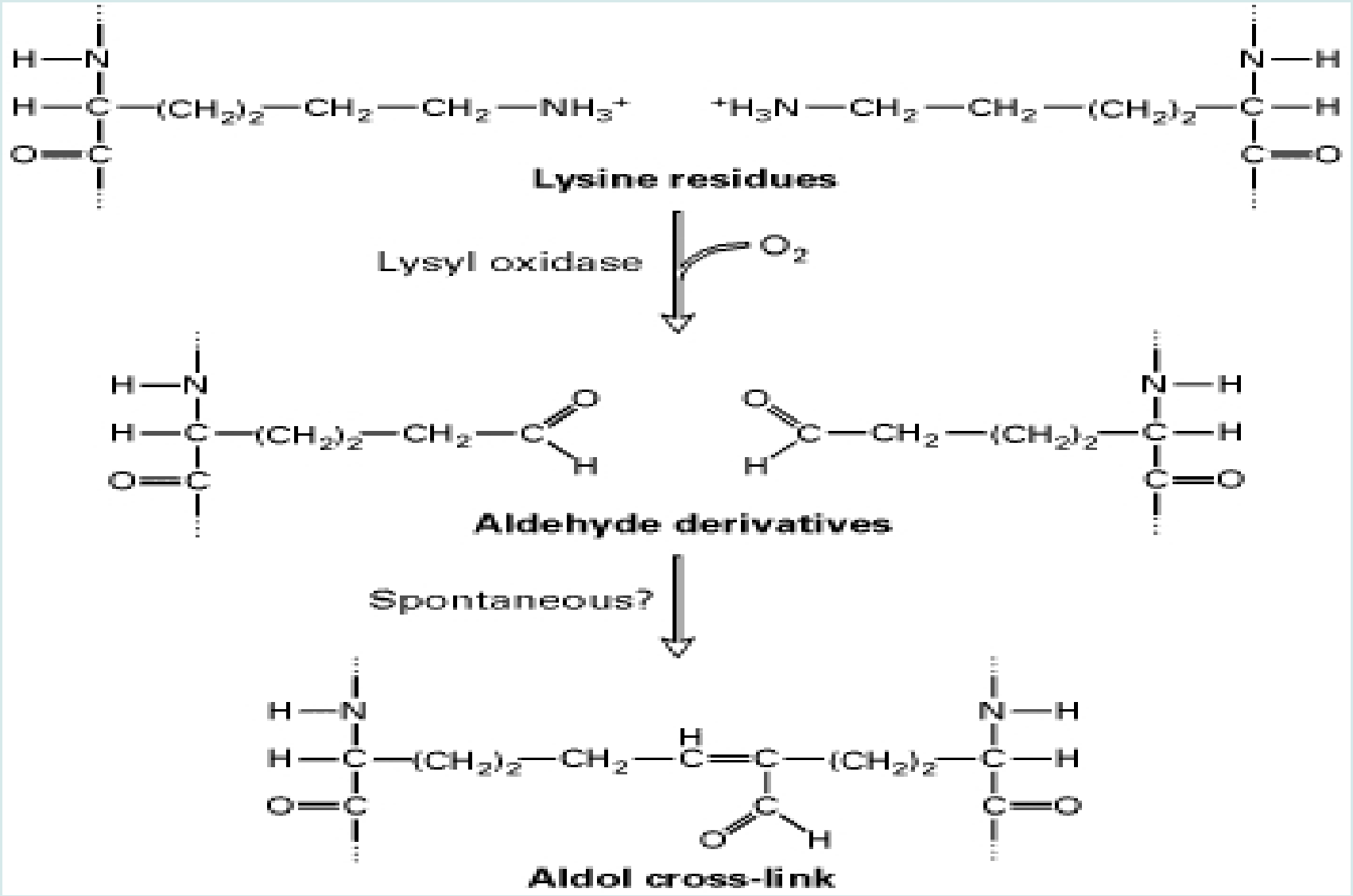
once outside the cell, membrane bound enzymes known as *collagen peptidases*, remove the "loose ends" of the procollagen molecule. What is left is known as tropocollagen.

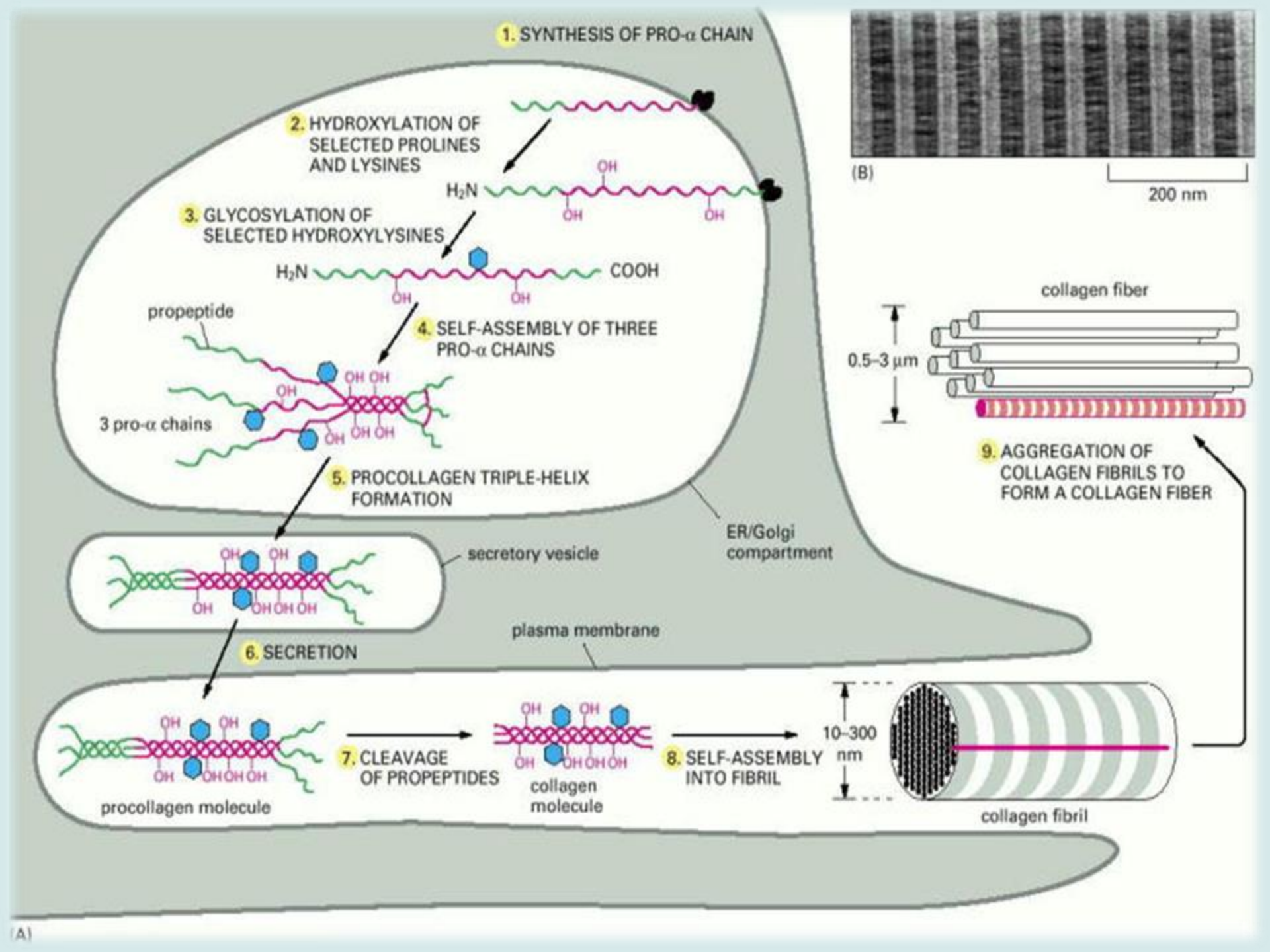
6- Formation of the Collagen Fibril:

-*Lysyl oxidase* and extracellular enzyme produces the final step in the collagen synthesis pathway.

-This enzyme acts on lysines and hydroxylysines producing aldehyde groups, which will eventually undergo covalent bonding between tropocollagen molecules. This polymer is known as a collagen fibril.

Some of the lysine side chains are oxidized to aldehyde derivatives, which react with another lysine or another oxidized lysine via the action of lysyl oxidase




1. SYNTHESIS OF PRO-α CHAIN
2. HYDROXYLATION OF SELECTED PROLINES AND LYSINES
3. GLYCOSYLATION OF SELECTED HYDROXYLYSINES
4. SELF-ASSEMBLY OF THREE PRO-α CHAINS
5. PROCOLLAGEN TRIPLE-HELIX FORMATION
6. SECRETION
7. CLEAVAGE OF PROPEPTIDES
8. SELF-ASSEMBLY INTO FIBRIL
9. AGGREGATION OF COLLAGEN FIBRILS TO FORM A COLLAGEN FIBER
propeptide
3 pro-α chains
secretory vesicle
ER/Golgi compartment
plasma membrane
procollagen molecule
collagen molecule
collagen fibril
collagen fiber
0.5–3 μm
10–300 nm
(A)
(B)
200 nm

Collagen linked diseases

Collagen-related diseases most commonly arise from genetic defects or nutritional deficiencies that affect the biosynthesis, assembly, postranslational modification, secretion, or other processes involved in normal collagen production.

In addition, certain autoimmune diseases such as rheumatoid arthritis may occur where the body's immune system perceives the collagen as foreign and attacks and degrades the collagen in the body.

Some bacteria and viruses also destroy collagen fibers in the body or interfere with its production.

Disorders of collagen synthesis (scurvy)

As is evident from the steps of collagen synthesis, Vitamin C forms an important component of the process.

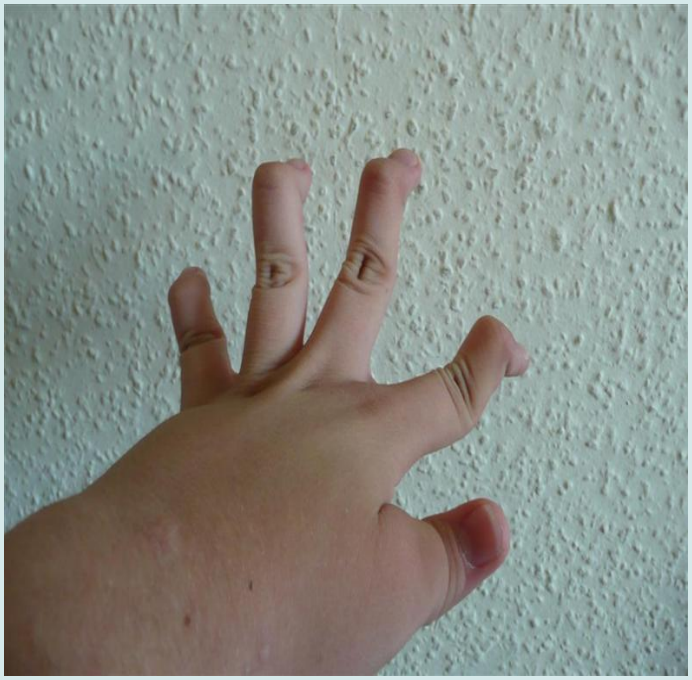
Vitamin C deficiency causes scurvy, a serious and painful disease in which the collagen that is synthesized is defective and it does not produce strong connective tissues.

This leads to bleeding and peeling gums, loss of teeth, skin discoloration and non-healing wounds.

Prior to the eighteenth century, this condition was notorious among long duration naval and military expeditions during which participants were deprived of foods containing Vitamin C.

type	notes	Gene(s)	Disorders
I	This is the most abundant collagen of the human body. It is present in scar tissue, the end product when tissue heals by repair. It is found in tendons, skin, artery walls, the endomysium of myofibrils, fibrocartilage, and the organic part of bones and teeth.	COL1A1, COL1A2	osteogenesis imperfecta, Ehlers-Danlos Syndrome, Infantile cortical hyperostosis aka Caffey's disease
II	Hyaline cartilage, makes up 50% of all cartilage protein. Vitreous humour of the eye.	COL2A1	Collagenopathy
III	This is the collagen of granulation tissue, and is produced quickly by young fibroblasts before the tougher type I collagen is synthesized. Reticular fiber. Also found in artery walls, skin, intestines and the uterus	COL3A1	Ehlers-Danlos Syndrome
IV	basal lamina; eye lens. Also serves as part of the filtration system in capillaries and the glomeruli of nephron in the kidney.	COL4A1, COL4A2, COL4A3, COL4A4, COL4A5, COL4A6	Alport syndrome, Goodpasture's syndrome
V	most interstitial tissue, assoc. with type I, associated with placenta	COL5A1, COL5A2, COL5A3	Ehlers-Danlos syndrome (Classical)
VI	most interstitial tissue, assoc. with type I	COL6A1, COL6A2, COL6A3	Ulrich myopathy and Bethlem myopathy

Ehlers-Danlos syndrome (EDS)



EDS is a group of inherited connective tissue disorders, caused by a defect in the synthesis of collagen (Type I or III). The collagen in connective tissue helps tissues resist deformation.

abnormal collagen leads to increased elasticity within these structures. Depending on the individual, the severity of the mutation can vary from mild to life-threatening.

Abnormalities in tenascin protein also lead to a form of Ehlers-Danlos syndrome.

Researchers suspect that tenascin could play a role in regulating the normal distribution of collagen in the connective tissues of the body.

Types of Ehlers-Danlos syndromes

Classical type

Marked joint hypermobility, skin hyperextensibility (laxity), and fragility are characteristic of the classic type of Ehlers-Danlos syndrome.

This classical type is inherited as an autosomal dominant genetic trait

Hypermobility type

Joint hypermobility is the major manifestation of this form of Ehlers-Danlos syndrome. Any joint can be affected, and dislocations are frequent.

This type is also inherited as an autosomal dominant genetic trait.

Vascular type (the arterial form)

In this form of Ehlers-Danlos syndrome, spontaneous rupture of arteries and bowel is a serious manifestation that can lead to death.

It is primarily inherited as an autosomal dominant genetic trait, but recessive trait inheritance has been described.

Kyphoscoliosis type

Fragile globe of the eyes, significant skin and joint laxity, and severe curvature of the spine (scoliosis) are typical features.
Its inheritance pattern is autosomal recessive.

Arthrochalasia type (arthrochalasis multiplex congenita)

Patients are short in height and severely affected by joint laxity and dislocations. Skin involvement is variable.

Both autosomal dominant and recessive inheritance is possible.

Dermatosparaxis type

Patients have severely fragile skin that is soft and doughy with sagging and folding. This rare form of Ehlers-Danlos syndrome can be diagnosed with a skin biopsy.

Tenascin-X deficient type

Joint hypermobility, hyperelastic skin, and fragile tissue are seen.

It is inherited as an autosomal recessive genetic trait.

Genetics of the disease

Mutations in the following can cause Ehlers–Danlos syndrome:

Fibrous proteins: COL1A1, COL1A2, COL3A1, COL5A1, COL5A2, and TNXB

Enzymes: ADAMTS2, PLOD1, B4GALT7

Mutations in these genes usually alter the structure, production, or processing of collagen or proteins that interact with collagen.

Inheritance patterns depend on the type of Ehlers–Danlos syndrome.

Most forms of the condition are inherited in an autosomal dominant pattern.

The minority are inherited in an autosomal recessive pattern, which means both copies of the gene must be altered for a person to be affected by the condition.

Collagenopathy

The type II and XI collagenopathies are a group of disorders that affect connective tissue. These disorders are caused by defects in type II or type XI collagen.

Type II and type XI collagen disorders are grouped together because both types of collagen are components of the cartilage found in joints and the spinal column, the inner ear, and the jelly-like substance that fills the eyeball.

Type II and XI collagenopathies result in similar clinical features.

Causes

Mutations in the *COL11A1*, *COL11A2*, and *COL2A1* genes cause collagenopathy, types II and XI.

Type II collagen is made by combining three copies of the alpha chain made by the *COL2A1* gene.

Type XI collagen, on the other hand, is composed of three different alpha chains: the products of the *COL2A1*, *COL11A1*, and *COL11A2* genes.

Collagenopathy, type 2 alpha 1:

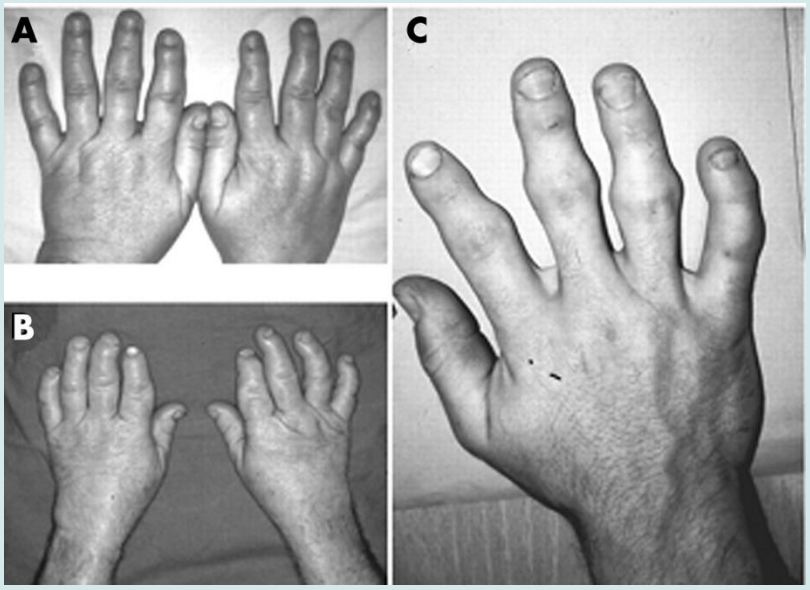
refers to a wide range of conditions that can result from problems with cartilage collagen tissue due to a defect in the COL2A1 gene.

Defects in the COL2A1 gene result in defective or reduced collagen production which in turn affects the development of connective tissues including bones.

Symptoms of Collagenopathy, type 2 alpha 1

<u>The list of signs and symptoms mentioned in various sources for Collagenopathy, type 2 alpha 1 includes the 10 symptoms listed below:</u>

Abnormal bone development
Short stature
Enlarged joints
Curved spine
Premature arthritis
Vision problems
Hearing problems
Cleft palate
Small lower jaw
Various facial anomalies



Alport syndrome

Alport syndrome or hereditary nephritis is a genetic disorder characterized by end stage kidney disease, and hearing loss.

Causes

Alport syndrome is caused by mutations in COL4A3, COL4A4, and COL4A5, collagen biosynthesis genes.

Mutations in any of these genes prevent the proper production or assembly of the type IV collagen network, which is an important structural component of basement membranes in the kidney, and inner ear

The disorder is uncommon. It most often affects males. Women can pass the gene for the disorder to their children, even if they have no symptoms.

Risk factors include:

End-stage kidney disease in male relatives

Hearing loss before age 30

Ullrich congenital muscular dystrophy

Ullrich congenital muscular dystrophy is a condition that mainly affects skeletal muscles.

Affected individuals show muscle weakness soon after birth. The muscle weakness is typically severe, and most affected people are not able to walk unassisted.

What genes are related to Ullrich congenital muscular dystrophy?

The genes responsible for Ullrich congenital muscular dystrophy have been identified and lie on chromosomes 21 and 2. These 3 genes are responsible for the production of the protein collagen VI.

Mutations in the *COL6A1*, *COL6A2*, and *COL6A3* genes cause Ullrich congenital muscular dystrophy. These genes each provide instructions for making one component of a protein called type VI collagen. This protein plays an important role in muscle, particularly skeletal muscle.