Amino acids in formation of collagen

Collagen contains specific amino acids – Glycine, Proline, Hydroxyproline.

The sequence often follows the pattern Gly-Pro-X or Gly-X-Hyp

Proline or hydroxyproline constitute about 1/6 of the total sequence. Proline consist of 17% of collagen.

Glycine (Gly) is found at almost every third residue. MOST APANDUNT AMINO ACID in collagen

Collagen metabolism and Chemistry of collagen

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

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.

Breakdown

Collagen degradation is less well-understood than collagen formation. 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.

Synthesis of collagen

1-Transcription of mRNA:

34 genes associated with collagen formation,

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: mRNA exit the nucleus to bind to ribosome subunits and the process of translation occurs.
-The early/first part of the new peptide is known as the signal sequence.

-signal sequence on the N-terminal of the pre-pro 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.

3- Alpha Peptide to Procollagen: from pre-pro peptide to procollagen
-Three modifications of the pre pro-peptide

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

B- Hydroxylation of lysines and prolines on propeptide by the enzymes *prolyl hydroxylase* and *lysyl hydroxylase* (hydroxyproline and hydroxylysine) -It is an enzymatic step that requires vitamin C as a cofactor.

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

****hydroxylated and glycosylated propeptide twists towards the left very tightly and then three propeptides will form a triple helix.**
- known as *procollagen*

4-Golgi Apparatus Modification
In the golgi apparatus, the procollagen oligosaccharides (not monosaccharides like in step 3) are added.

5- Formation of tropocollagen: -*collagen peptidases*, remove the "loose ends" of the procollagen molecule. What is left is as known tropocollagen

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.

Collagen linked diseases

-Disorders of collagen synthesis (scurvy) :

Vitamin C deficiency causes scurvy, a serious and painful disease in which the collagen that is synthesized is defective

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) .

types of Ehlers-Danlos syndromes

Classical type :Marked joint hypermobility, his classical type is inherited as an autosomal dominant genetic trait .

Hypermobility type Joint hypermobility this type is also inherited as an autosomal dominant genetic trait.

Vascular type (the arterial form) In this form, spontaneous rupture of arteries . primarily inherited as an autosomal dominant genetic trait.

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. Both autosomal dominant and recessive inheritance is possible.

Dermatosparaxis type Patients have severely fragile skin

Tenascin-X deficient type joint hypermobility, hyperelastic skin, It is inherited as an autosomal recessive

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

Most forms of the condition are inherited in an autosomal dominant

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

Causes : Mutations in the *COL11A1*, *COL11A2*, and *COL2A1* genes

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.

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,

ullrich congenital muscular dystrophy

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

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.

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