Biochemistry(1):-

Types of proteins:

① Globular proteins

② Fibrous proteins → collagen and elastin.

↳ most common fibrous proteins presenting in human body.

⇒ Collagen is the most common protein in human body.

tendons - bones - cartilages بدخل في تكوين الـ

↳ collagenopathies

integumentary واحد عنده مشكلة في الـ
في skin الـ / system

⊕ Ehler-Danlos #

⊕ Osteogenesis imperfecta.

OVERVIEW

Collagen and elastin are examples of common, well-characterized fibrous proteins of the extracellular matrix that serve structural functions in the body.

For example, collagen and elastin are found as components of skin, connective tissue, blood vessel walls, and the sclera and cornea of the eye. Each fibrous protein exhibits special mechanical properties, resulting from its unique structure, which is obtained by combining specific amino acids into regular, secondary structural elements.

Types of collagen → more than 25 types.

[categories according to collagen arrangement]

لوهل هو Fibril ولا بساعدني تكوين network/meshwork.

Fibrilولا عامل

COLLAGEN

Collagen is the most abundant protein in the human body. A typical collagen molecule is a long, rigid structure in which three polypeptides (referred to as α chains) are wound around one another in a rope-like triple helix.

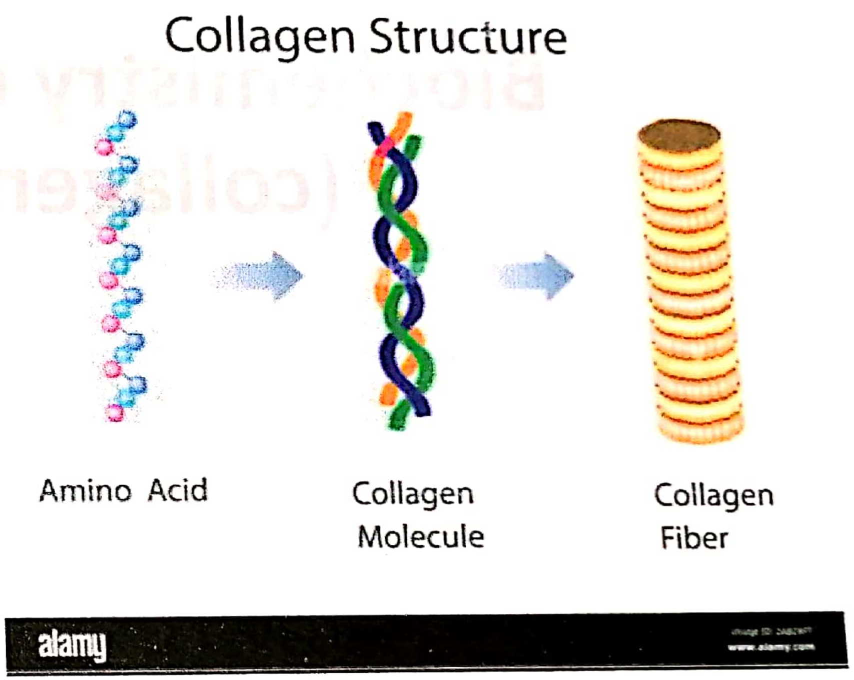
↳ 3 chains [α-chains]

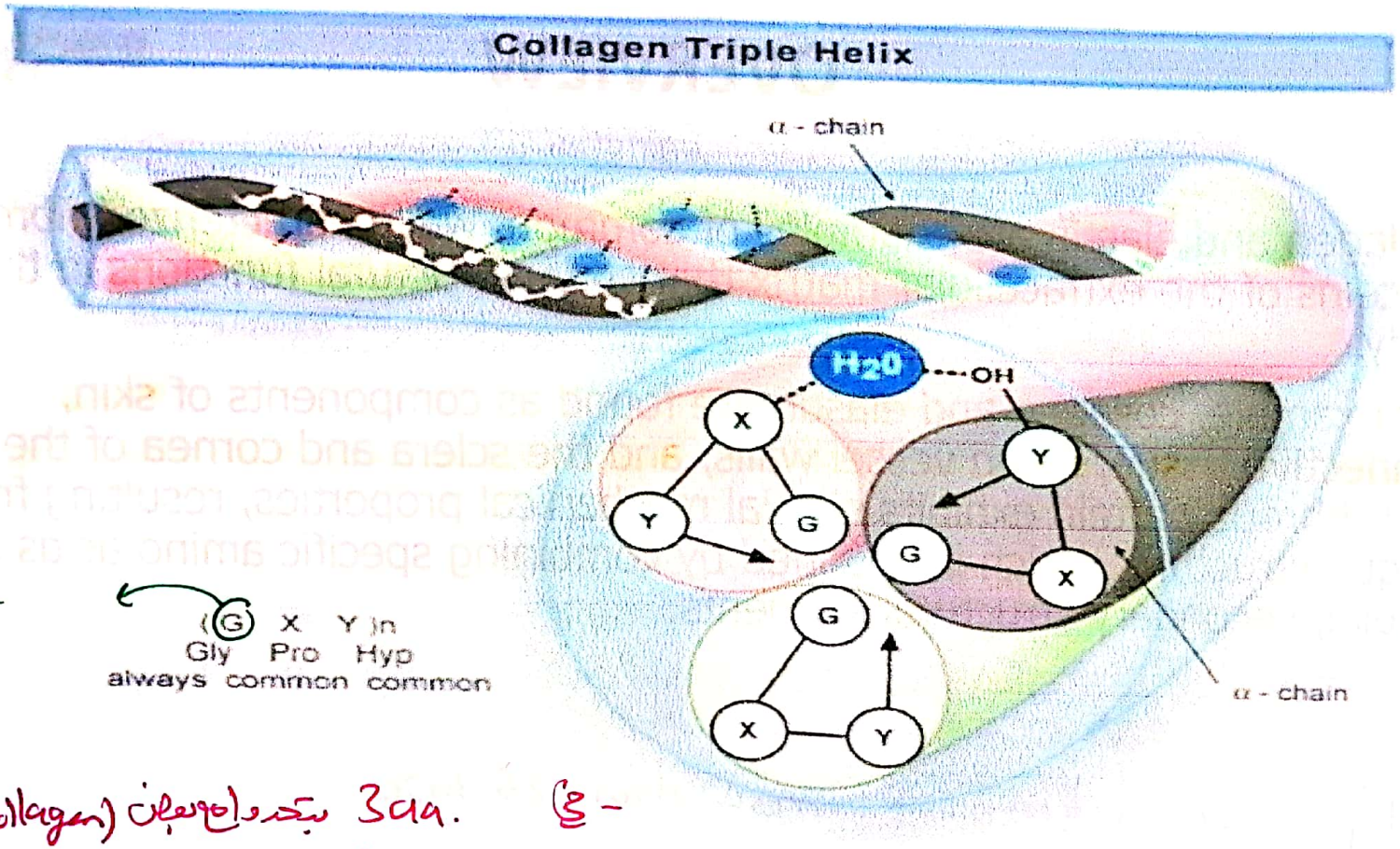
لو شيار طالع يتحدد نوع ال collagen الي بطلع
في α_1 و α_2

ممكن تطلع $\alpha_1\alpha_1\alpha_2$ / $\alpha_1\alpha_1\alpha_1$

وهكذا. هاي تطلع ال molecular
of collagen.

- هاي الوحدة البنائية لل collagen / بصير transcription
وبالآخر يطلعوا البروتين.





glycine
تابتة

(G) X Y in
Gly Pro Hyp
always common common

(Base unit of collagen) بتتكون من 3aa. في -

aa - aa - glycine يعني ثابت glycine الـ

. glycine داخل 3rd position الـ

↳ 33% / $\frac{1}{3}$ of all aa in collagen.

Glycine is a fixed aa. in the 3rd position.

Hydroxyproline [Hyp] و proline الاثنين التانيين الموجودين لافي common يكونوا ها

لكن ممكن نلاقي glycine - lysine و hydroxylysine

⇒ Glycine - proline - Hydroxyproline are common

صح دايما موجودين لكنهم common → 20 - 35% موجودين

+ ممكن نلاقي lysine و hydroxylysine

- ↳ hydroxylation of lysine
- ↳ only presents in collagen.

فأول ما نشوف hydroxylysine معناها هاد البروتين هو collagen.

المسوحة ضوئيا بـ CamScanner

.(α2 - α1) الانواع، الانواع تعتمد على ال chain الموجودة

Although these molecules are found throughout the body, their types and organization are dictated by the structural role collagen plays in a particular organ.

In some tissues, collagen may be dispersed as a gel that gives support to the structure, as in the extracellular matrix or the vitreous humor of the eye.

In other tissues, collagen may be bundled in tight, parallel fibers that provide great strength, as in tendons.

In the cornea of the eye, collagen is stacked to transmit light with a minimum of scattering. → ترتيبة تسمح بدخول ال light لل cornea

Collagen of bone occurs as fibers are arranged at an angle to each other to resist mechanical shear from any direction.

في بنائها عاملين angles مع بعض وهاد بقويه أكثر

يعني ال right angles أقوى ما يكون هاد ال collagen الموجود

في ال bones . الثاني بكون parallel وهكذا.

اذا ترتيب ال collagen (هو نفس ال collagen في كله) ولكن

الترتيب الي بختلف و بحدد مكان تواجده.

A. Types (3 types) → Fibril Forming – network forming – Fibril-associated

The most common عا.

The collagen superfamily of proteins includes more than 25 collagen types as well as additional proteins that have collagen-like domains. The three polypeptide α chains are held together by interchain hydrogen bonds.

Variations in the amino acid sequence of the α chains result in structural components that are about the same size (approximately 1,000 amino acids long) but with slightly different properties.

These α chains are combined to form the various types of collagen found in the tissues. For example, the most common collagen, type I, contains two chains called α1 and one chain called α2 (α12α2), whereas type II collagen contains three α1 chains (α13). The collagens can be organized into three groups, based on their location and functions in the body

$\alpha_2 - \alpha_1$ ← (α-chains) بالآخر حيطلعت

هادا اللي بحدد أي نوع

① النوعة المجموعة من type I

1 α2 chain – 2 α1 chains

يعني بثلاثي بثلاثي منها ← Type I collagen وهادا له أماكن خاصة فيه.

1. Fibril-forming collagens:

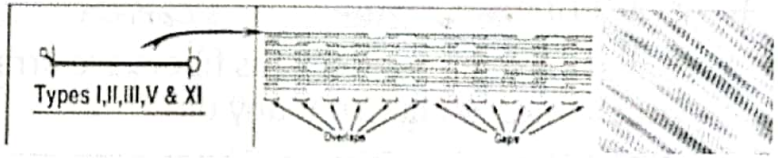
Types I, II, and III are the fibrillar collagens and have the rope-like structure described above for a typical collagen molecule. In the electron microscope, these linear polymers of fibrils have characteristic banding patterns, reflecting the regular staggered packing of the individual collagen molecules in the fibril.

Type I collagen fibers (composed of collagen fibrils) are found in supporting elements of the high tensile strength (for example, tendon and cornea), whereas fibers formed from type II collagen molecules are restricted to cartilaginous structures. The fibers derived from type III collagen are prevalent in more distensible tissues such as blood vessels.

Classification of collagen

1. Fibril-forming collagens

- No interruptions in triple helix
- Regular arrangement results in characteristic "D" period of 67 nm
- Diameter : 50-500 nm
- Example : Types I, II, III, V, XI



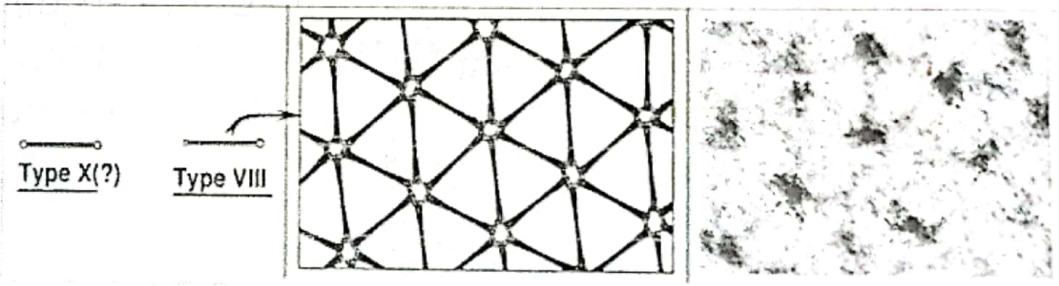
2. Network-forming collagens:

Types IV and VIII form a three-dimensional mesh, rather than distinct fibrils. For example, type IV molecules assemble into a sheet or meshwork that constitutes a major part of basement membranes.

Classification of collagen

2. Network-forming collagens

- Forms network in basement (Collagen IV) and Descemet's membrane (Collagen VIII)
- Molecular filtration
- Example : Types IV, VIII, X



3. Fibril-associated collagens:

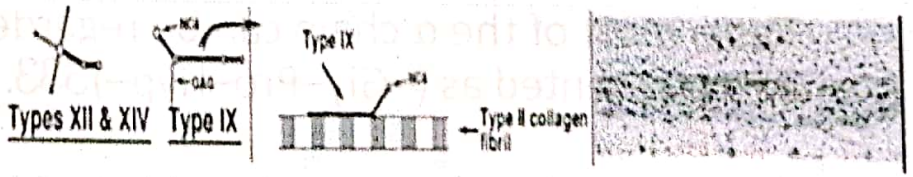
Types IX and XII bind to the surface of collagen fibrils, linking these fibrils to one another and to other components in the extracellular matrix

بكل عبارة عنا
من المجموعة الأولى type I
type صار branches, انضاف عليها
من المجموعة الثالثة IX - XII - XIV

Classification of collagen

3. Fibril-associated collagens with interrupted triple helices (FACITs)

- Short collagens with interruptions
- Linked to collagen II and carries a GAG chain
- Found at the surface of fibril-forming collagens
- Example : Types IX, XII, XIV



TYPE	TISSUE DISTRIBUTION
	Fibril-forming
I	Skin, bone, tendon, blood vessels, cornea
II	Cartilage, intervertebral disk, vitreous body
III	Blood vessels, skin, muscle
	Network-forming
IV	Basement membrane
VIII	Corneal and vascular endothelium
	Fibril-associated*
IX	Cartilage
XII	Tendon, ligaments, some other tissues

Figure 4.2: The most abundant types of collagen. *Known as FACITs: fibril-associated collagens with interrupted triple helices.

لـ ما كانت موجودة في النوع الاول

مشابهة للنوع الأول
لأنه هو نفسه بس إجاتوه
بسلاسل جانبية
لكن ال Fibril associated هو ال most common بينهم tissue مشتركة

B. Structure

1. **Amino acid sequence:** Collagen is rich in proline and glycine, both of which are important in the formation of the triple-stranded helix. Proline facilitates the formation of the helical conformation of each α chain because its ring structure causes "kinks" in the peptide chain

→ most common.

Glycine, the smallest amino acid, is found in every third position of the polypeptide chain. It fits into the restricted spaces where the three chains of the helix come together. The glycine residues are part of a repeating sequence, –Gly–X–Y–, where X is frequently proline, and Y is often hydroxyproline (but can be hydroxylysine). Thus, most of the α chain can be regarded as a polytripeptide whose sequence can be represented as (–Gly–Pro–Hyp–)333.

→ specific to collagen.

أما elastin فسكيل تالاتيه.

Triple fibrous protein - not globular

2. **Triple-helical structure:** Unlike most globular proteins that are folded into compact structures, collagen, a fibrous protein, has an elongated, triple-helical structure that is stabilized by interchain hydrogen bonds.

← يمكن يكون Fibril أو networking

in 1st and 2nd position [Hydroxylation is most in the 2nd]

3. **Hydroxyproline and hydroxylysine:** Collagen contains hydroxyproline and hydroxylysine, which are not present in most other proteins. These residues result from the hydroxylation of some of the proline and lysine residues after their incorporation into polypeptide chains.

Hydroxylation is, thus, an example of posttranslational modification. [Note: Generation of hydroxyproline maximizes formation of interchain hydrogen bonds that stabilize the triple-helical structure.]

Hydroxyproline can be presented in elastin.

galactose أو glucose يا بنضيف collagen بس في elastin لا

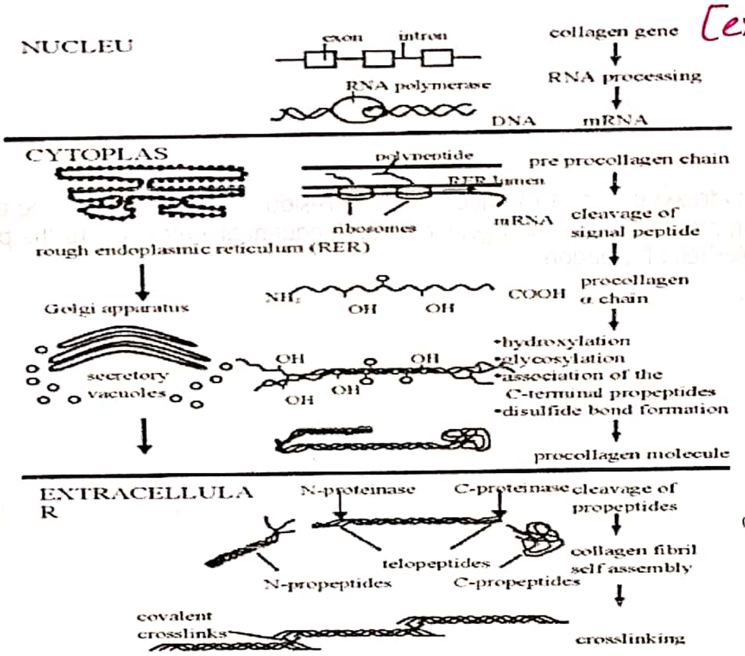
Glycosylation: The hydroxyl group of the hydroxylysine residues of collagen may be enzymatically glycosylated. Most commonly, glucose and galactose are sequentially attached to the polypeptide chain prior to the triple-helix formation

Steps in collagen biosynthesis

- Transcription [mRNA].
- Translation on rough ER and entry into ER to form α chain protein
- Hydroxylation in the ER (needs vit C)
  - ↳ في الجسم → so, vitamin C has a role in collagen synthesis
  - → so, deficiency in vitamin C [scurvy] يسبب to hydroxylation. في
- Triple helix assembly
- Glycosylation, transport to Golgi, further glycosylation
- Secretion
- Removal of propeptides ← N-terminal C-terminal الأحماض الأمينية.
- Assembly into fibrils
- Crosslinking

scurvy → Friable collagen.

hydroxylysine. → hydroxyproline هيدروكسيليشن hydroxylation لأنه على

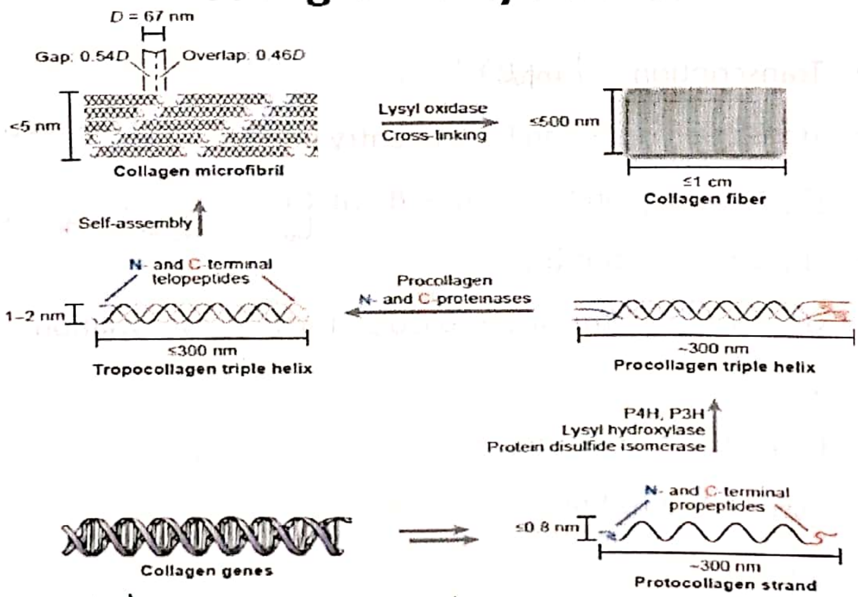


[exon - intron].

[N and C terminal] ↓ بنشالوا بنشكل دهاعافي ال extracellular matrix by peptidase وبيكون عن ال propeptide

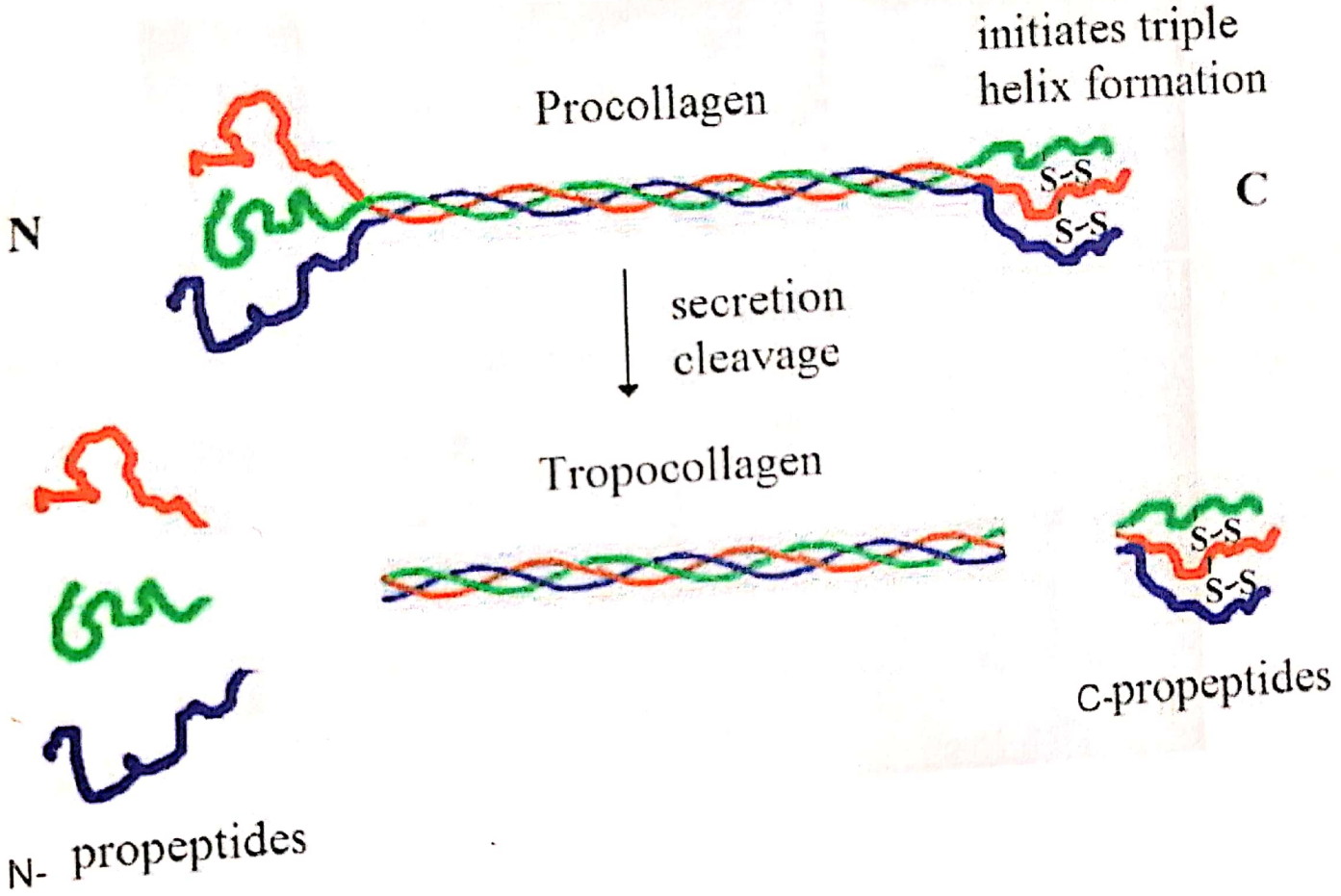
[Fibril protein] وبصير له allembly

Collagen biosynthesis



هاد في ال nucleus ودال cytoplasm

Transcription → precollagen chain → cleavage of single peptide → procollagen α chain تكون → α chain 3 –
procollagene glycosylation & hydroxylation by vit C. ← بتكون عوضها



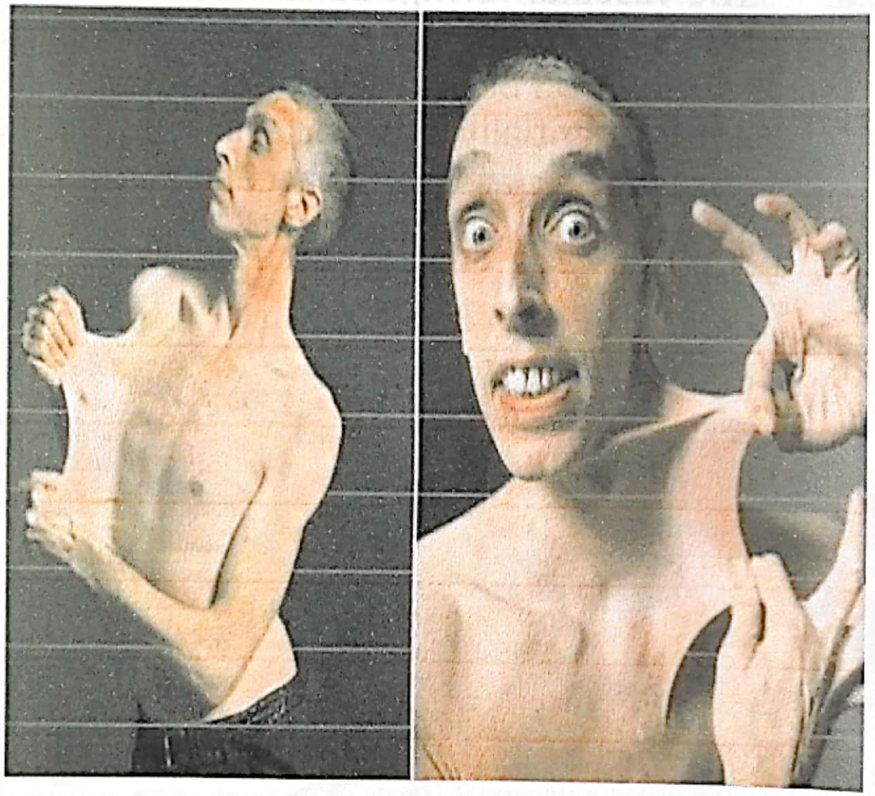
Collagen diseases: Collagenopathies

1. Ehlers-Danlos syndrome: autosomal dominant.

Ehlers-Danlos syndrome (EDS) is a heterogeneous group of connective tissue disorders that result from inheritable defects in the metabolism of fibrillar collagen molecules.

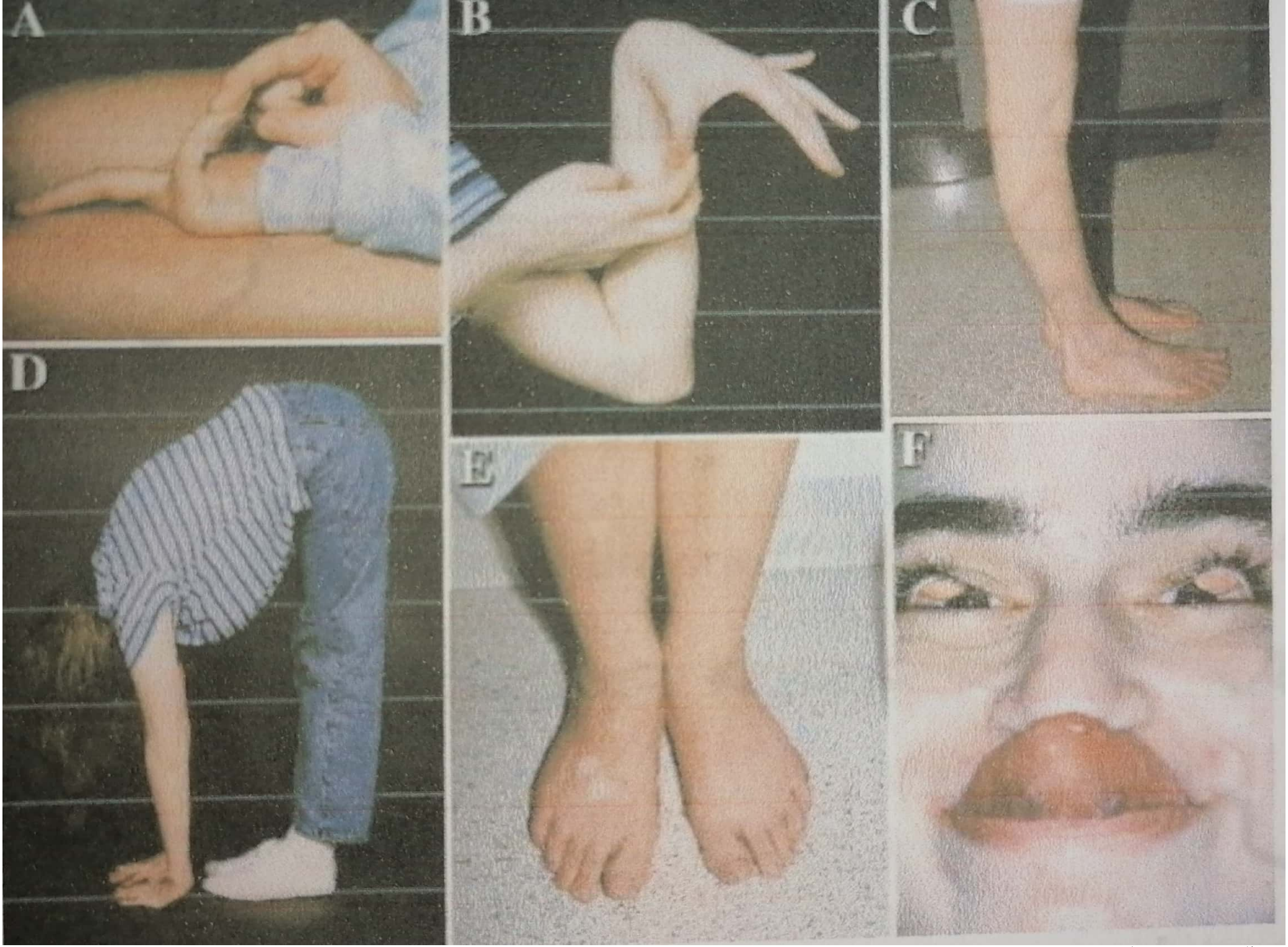
EDS can be caused by a deficiency of collagen-processing enzymes (for example, lysyl hydroxylase or N-procollagen peptidase) or from mutations in the amino acid sequences of collagen types I, III, or V.

The classic form of EDS, caused by defects in type V collagen, is characterized by skin extensibility and fragility and joint hypermobility



.غيابي N-peptide ال

-type V → in skin



Fragile ← بتكون blood vessel بيكونوا هدول المرضى من مشكلة في ال

بصيرلها dilatation فبتكون aneurysm ← ممكن يكون في أي مكان

في الجسم - Coronary - thoracic aneurysm - abdominal aorta

الدماغ. ب Circle of Willis ← خصوصاً rupture aneurysm فيه أكثر إشي لكن ممكن في أي مكان.

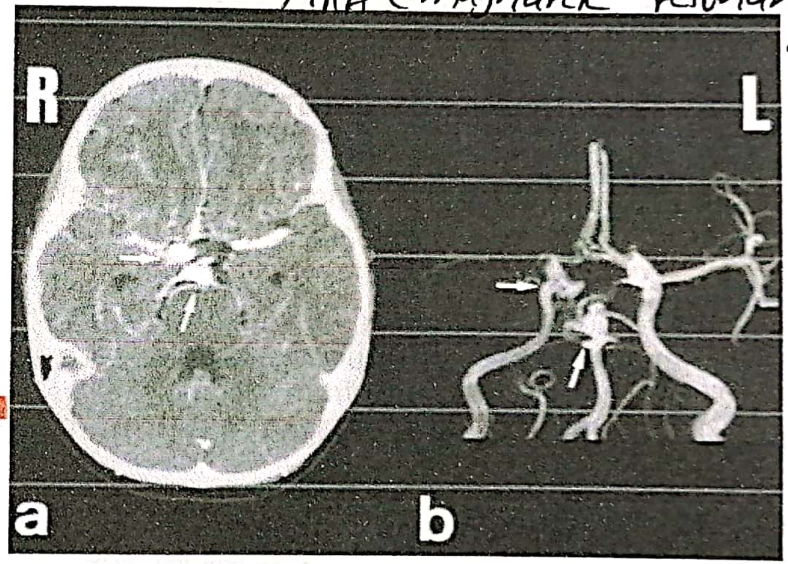
The vascular form, due to defects in type III collagen, is the most serious form of EDS because it is associated with potentially lethal arterial rupture. [Note: The classic and vascular forms show autosomal dominant inheritance.]

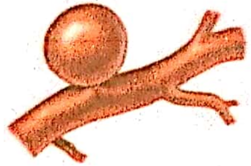
في كل الأنواع بيكونوا فيه

EDs has 5 types

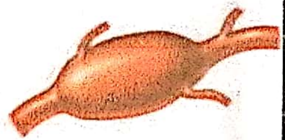
منهم مهمين.

MRA [magnetic resonance angiography]





Saccular Aneurysm



Fusiform Aneurysm

Ruptured Aneursym

أنواع ال aneurysm ←

saccular - Fusiform - Rupture

+ في False بيكون في injury لل intima ما بيكون true aneurysm حاصل dilation

بلشها injury to intima ودخل الدم فيها فتوسع

liver diseases - hemophilia C ← autosomal recessive أشياء

autosomal dominant ← cancers ⇐

↳ Wilson disease - Hemochromatosis - α1 anti-trypsin.

2. Osteogenesis imperfecta:

inheritance is according to its type, but mostly autosomal dominant.

العظم الزجاجي

This syndrome, known as brittle bone disease, is a genetic disorder of bone fragility characterized by bones that fracture easily, with minor or no trauma. Over 80% of cases of osteogenesis imperfecta (OI) are caused by dominant mutations to the genes that code for the α1 or α2 chains in type I collagen. → in bone.

The most common mutations cause the replacement of glycine (in –Gly–X–Y–) by amino acids with bulky side chains. The resultant structurally abnormal α chains prevent the formation of the required triple-helical conformation. Phenotypic severity ranges from mild to lethal.

لأنه ال glycine مميز.

↳ in utero [بموتوا وهم أجنة]

↳ type 2.

لما يموتوا من

pulmonary complication

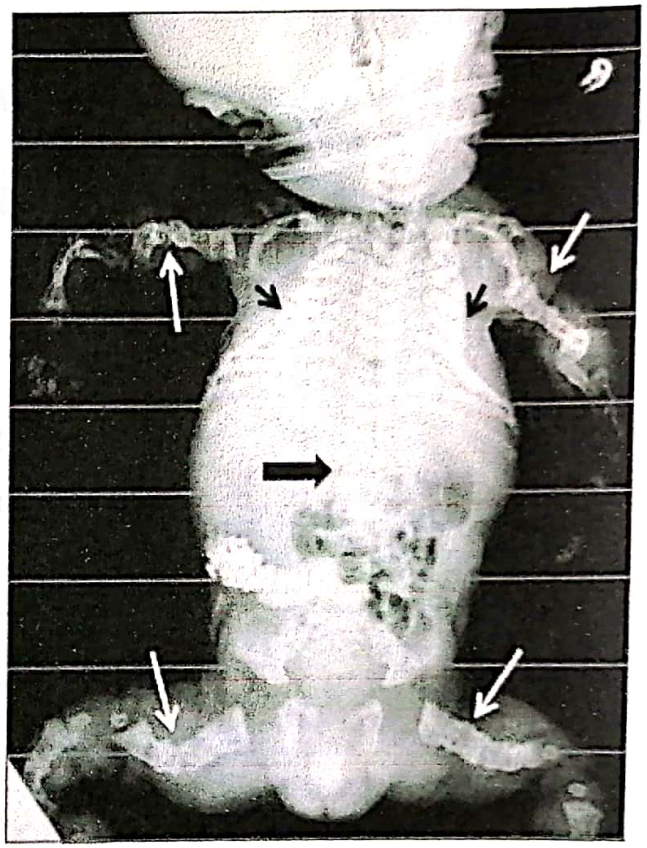
Type I OI, the most common form, is characterized by mild bone fragility, hearing loss, and blue sclerae.

Type II, the most severe form, is typically lethal in the perinatal period as a result of pulmonary complications. In utero fractures are seen.

type 2 بعد

Type III is also a severe form. It is characterized by multiple fractures at birth, short stature, spinal curvature leading to a "humped-back" (kyphotic) appearance, and blue sclerae. Dentinogenesis imperfecta, a disorder of tooth development, may be seen in OI.

- Blue sclera can be normal
- Blue sclera → iron deficiency anemia
  OI في blue sclera



kyphosis → انحناء
Lordosis → لورا
scoliosis → lateral [S]

Mutations of OI

- Mutations in the *COL1A1* and *COL1A2* genes cause OI (85-90%)
- These mutations typically interfere with the assembly of type I collagen molecules
- A defect in the structure of type I collagen weakens connective tissues, particularly bone, resulting in the characteristic features of OI
- OI types **I, II, and IV** have an autosomal dominant pattern of inheritance (35%=sporadic)

Table

Types of Osteogenesis Imperfecta Based on Modified Sillence Classification[a]

Type	Severity	Mutation	Inheritance
I	Mild deformity	COL1A1/2	AD
II	Lethal in utero	COL1A1/2	AD
III	Severe deformity	COL1A1/2	AD
IV	Moderate deformity	COL1A1/2	AD
V	Moderate deformity	Unknown	AD
VI	Moderate–severe deformity	Unknown	AR
VII	Moderate deformity	CRTAP	AR
VIII	Severe deformity–lethal	LEPRE1	AR

Abbreviations: AD, autosomal dominant; AR, autosomal recessive.
[a]*Data from Van Dijk et al.*[9]

بكتبوا أول حاجة most severe compatable with life.

SYMPTOMS: (according to types)

type V, IV هو moderate deformity بكبروا عادي وهما صغار بيكسروا أكثر. ← ❑ multiple, frequent fractures → common according to type.

❑ muscle weakness

❑ curved bones

❑ Scoliosis

❑ brittle teeth

❑ short stature

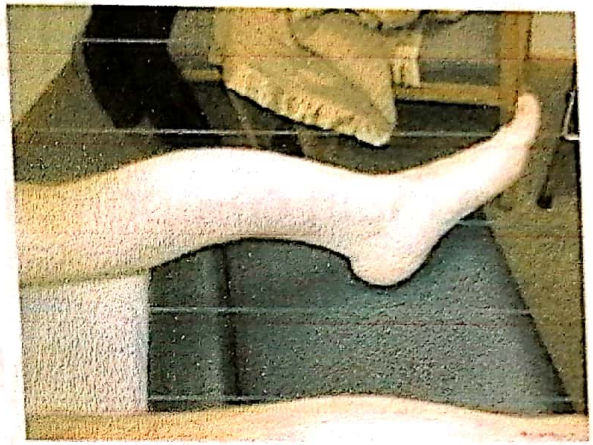
❑ blue sclera

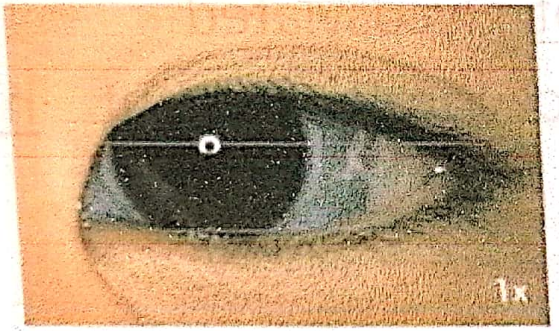
❑ fragile skin

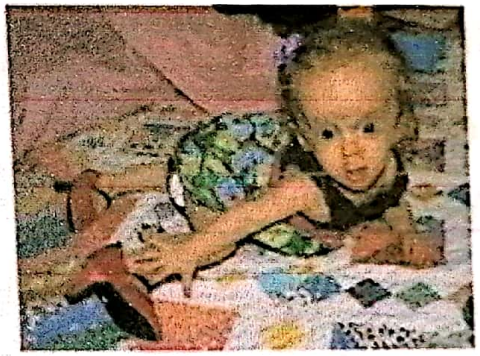
❑ triangular head and face shape

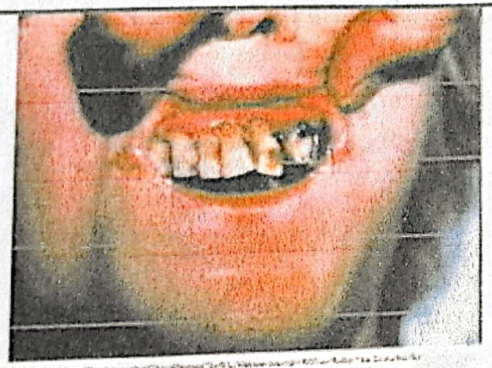
↳ due to delayed closure of fontanelle

لـ في anterior وفي posterior الزوايا يسكروا لما يطولوا لما يسكروا ما بتكبر عنده ال space بسوار بـ brain الـ Fluid ما بزيد عنهم ما بكبراسهم محتوى وصل تحت ثابت.









Scurvy (الأسقربوط)

Deficiency of vitamin C (ascorbic acid [hydroxylation of procollagen]) results in insufficient hydroxylation of procollagen and, hence, poor synthesis of collagen, formation of unstable triple helices preventing formation of normal fibrils

Non-hydroxylated procollagen chains are then degraded within the cell

This results in weakening of the collagen resulting in skin and gum lesions and weak blood vessels

↳ Friable collagen → easily injuried or bleeding person. / bruise.

Elastin [2nd fibrous protein].

- The main component of elastic fibers is elastin
- A highly hydrophobic protein, which, like collagen, is rich in proline and glycine
- But, unlike collagen, is not glycosylated
- Contains some hydroxyproline but no hydroxylysine

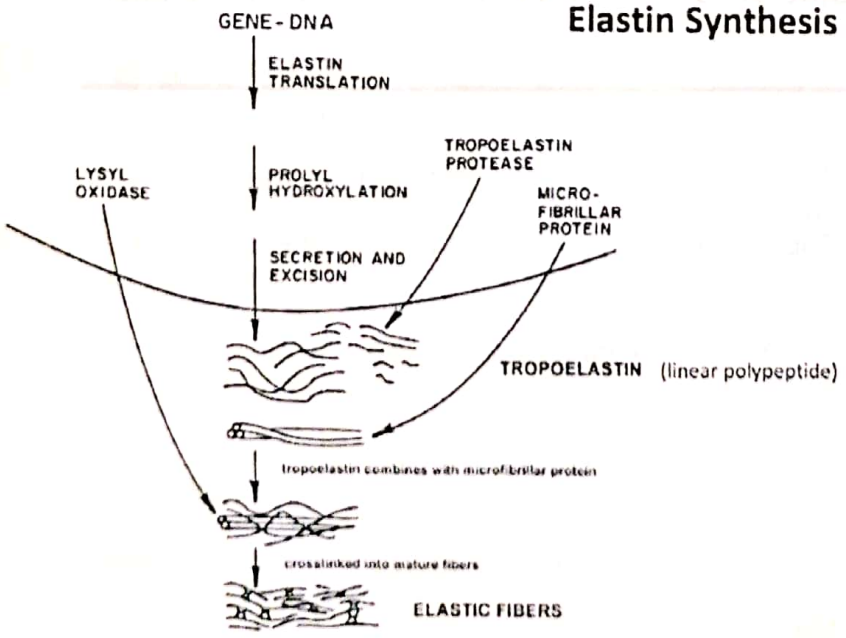
Formation of elastic network

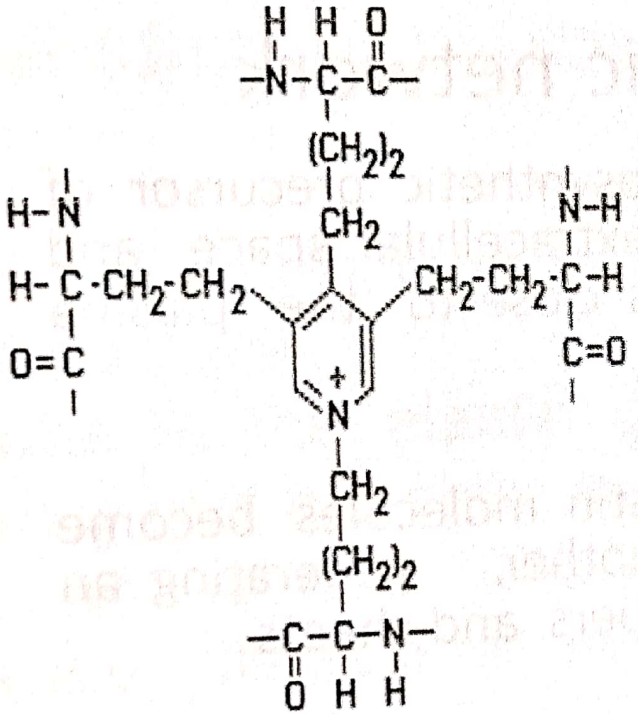
Soluble tropoelastin (the biosynthetic precursor of elastin) is secreted into the extracellular space and assembled into elastic fibers close to the plasma membrane

After secretion, the tropoelastin molecules become highly cross-linked to one another, generating an extensive network of elastin fibers and sheets

The cross-links are formed between lysines by a mechanism similar to that of collagen molecules

cross-linking في desmosine بساعد يكون collagen بشبه
elastin لـ .





Desmosine

- After secretion and alignment with ECM fibrils, numerous K residues are oxidized by lysyl oxidase, a reaction which initiates cross-linking of elastin monomers.
- the process is unique in that three lysine-derived aldehydes (allysyl) cross-link with an unmodified lysine forming a tetrafunctional structure called a desmosine.
- The highly stable cross-linking of elastin is what ultimately imparts the elastic properties to elastic fibers.

Table 47–5. Major differences between collagen and elastin.

Collagen	Elastin
1. Many different genetic types	One genetic type
2. Triple helix	No triple helix; random coil conformations permitting stretching
3. $(Gly\text{-}X\text{-}Y)_n$ repeating structure	No $(Gly\text{-}X\text{-}Y)_n$ repeating structure → glycine كثيرة
4. Presence of hydroxylysine	No hydroxylysine
5. Carbohydrate-containing	No carbohydrate
6. Intramolecular aldol cross-links ← H- bonds	Intramolecular desmosine cross-links
7. Presence of extension peptides during biosynthesis	No extension peptides present during biosynthesis

Function of elastic fiber

- Elastin is the dominant extracellular matrix protein in arteries
- Mutations in the elastin gene causing a deficiency of the protein result in narrowing of the aorta or other arteries as a result of excessive proliferation of smooth muscle cells in the arterial wall

← مشكلة ال elastin بصير في Friability in blood vessels.

lateral narrowing then dilatation

صح aneurysm لكن مش narrowing لل elastin الذي يعتبر main component of blood vessels مع ال collagen.

- Most common blood vessel → aorta.

Diseases of Elastic Fiber

[Elastinopathies]

- Williams syndrome
- Marfan's syndrome (fibrillin)

Williams Syndrome

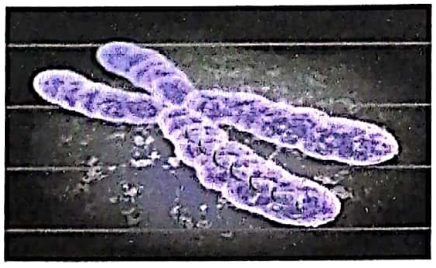
- Autosomal dominant disorder
- Occurs in approximately one of every 20,000 births
- Variability in expressivity

هاد commonly سنتكلم بكونغي الـ aorta.

Overall Cause

- Spontaneous deletion on chromosome band 7q11.23.
- Deletion removes more than 25 genes that encode for different functions.

أساسيين في تكوين الـ elastin



Physical Characteristics: elfin

Facial Characteristics

- broad forehead
- flattened nasal bridge
- wide mouth,
- Full cheeks
- puffiness around the eyes
- long philtrum
- Voice: hoarse, abnormal vocal cord elastin

home.sc.rr.com/cmindel/

Problems associated with WS

- Heart & Blood Vessel Defects
- Supravalvular aortic stenosis (73%) ← ممكن يكون valvular — infravalvular
- High blood pressure → due to stenosis.
- Hypercalcemia(15%) $(\frac{1}{7})$ 1/7 persons.

(*) aortic stenosis ⟶ supravalvular – valvular – infravalvular
↳ acyanotic heart disease

بتوصل heart failure لانه aorta مسكر فبصير
lt ventricular hypertrophy → HF.

Cyanotic - non-cyanotic ← (تقسيم في الولادة) congenital heart disease الـ NS

لـ سواد أول ما الولد أول بعد فترة

بكون الدم الموجود في الـ RL

RL side الـ يمين الـ side

[deoxygenated to oxygenated] → deoxygenated blood in aorta → cyanosis.

* most common syndrome causing cyanosis is ← Tetralogy of Fallot

لـ صبح بعد الولادة على طول.

More Symptoms

- Low birth weight, feeding problems
- kidney abnormalities (Stenosis of the renal arteries)
- hearing sensitivity
- musculoskeletal problems
- Overly friendly but has learning disabilities and usually are mildly retarded [IQ < 70-80]

- VSD
- pulmonary stenosis
- overriding aorta
- RL ventricular hypertrophy.

* Cyanotic heart disease [T] → Transportation of great vessels - Total anomalous pulmonary venous return - Tetralogy of Fallot - Tricuspid atresia

* Acyanotic ← ASD - VSD - AVSD —— / bicuspid valve stenosis - PDA.

Some examples

Diagnosis

- Diagnosis of Williams syndrome begins with recognition of physical symptoms

- fluorescent in situ hybridization (FISH) test

لكشف شذوذ الكروموسوم و الـ gene mutation

لكن صعب

A 7-month-old child "fell over" while crawling and now presents with a swollen leg.

Imaging reveals a fracture of a bowed femur, secondary to minor trauma, and thin bones). Blue sclerae are also noted. At age 1 month, the infant had multiple fractures in various states of healing (right clavicle, right humerus, and right radius). A careful family history has ruled out nonaccidental trauma (child abuse) as a cause of the bone fractures. Which pairing of a defective (or deficient) molecule and the resulting pathology best fits this clinical description?

A. Elastin and emphysema

B. Fibrillin and Marfan disease

C. Type I collagen and osteogenesis imperfecta (OI)

D. Type V collagen and Ehlers-Danlos syndrome (EDS)

E. Vitamin C and scurvy

non-accidental trauma
أول إشي بيعرفك إذا هو
child abuse
ولا لا.

Correct answer = C. The child most likely has osteogenesis imperfecta. Most cases arise from a defect in the genes encoding type I collagen. Bones in affected patients are thin, osteoporotic, often bowed, and extremely prone to fracture. Pulmonary problems are not seen in this child. Individuals with Marfan syndrome have impaired structural integrity of the skeleton, eyes, and cardiovascular system. Defects in type V collagen cause the classic form of EDS characterized by skin extensibility and fragility and joint hypermobility. Vitamin C deficiency is characterized by capillary fragility.