Marfan Syndrome
Inborn errors in metabolism

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Collage of science
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Biosynthesis of Collagen

NUCLEUS

- exon
- intron
- RNA polymerase
- DNA
- mRNA
- collagen gene
- RNA processing

CYTOPLASM

- polypeptide
- RER lumen
- ribosomes
- mRNA
- cleavage of signal peptide
- pre procollagen chain
- rough endoplasmic reticulum (RER)
- Golgi apparatus
- NH₂ OH OH COOH α chain
- OH OH OH
- hydroxylation
- glycosylation
- association of the C-terminal propeptides
- disulfide bond formation
- procollagen molecule
- secretory vacuoles

EXTRACELLULAR MATRIX

- N-proteinase
- C-proteinase
- cleavage of propeptides
- collagen fibril
- self assembly
- N-propeptides
- telopeptides
- C-propeptides
- covalent crosslinks
- crosslinking
Collagen biosynthesis

1. Transcription in nucleus
2. Translation of preprocollagen in RER
3. Hydroxylation in RER
4. Glycosylation in RER
5. Formation of procollagen triple helix in RER
6. Secretion of procollagen via trans Golgi network
7. Cleavage of propeptides to form tropocollagen molecule
8. Spontaneous self-assembly of tropocollagen to form collagen fibril
Biosynthesis of Collagen

1. Rough ER
2. Propeptide
3. Hsp47
4. Lateral association
5. Golgi complex
6. Extracellular space
7. Propeptide cleavage
8. Fibril assembly and crosslinking

Collagen molecule

Collagen fibril

Cross-striations (67 nm)

250 nm

67 nm
Packing of types II, XI, and IX collagen in the cartilage collagen heterofibril, showing the location of the covalent cross-links between type II and IX collagen. The globular NC4 domains of type IX collagen reach out of the fibril. (From D. Eyre (2001)
<table>
<thead>
<tr>
<th>Type</th>
<th>Subunits</th>
<th>Molecular forms</th>
<th>Tissue distribution</th>
<th>Characteristic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>α1(I) α2(I)</td>
<td>α1(I)₂ α2</td>
<td>Bone, dermis, tendon, ligaments, cornea, most other tissues</td>
<td>Forms fibers of high tensile strength; most abundant collagen</td>
</tr>
<tr>
<td>I</td>
<td>α1(I)</td>
<td>[α1(I)]₃</td>
<td>Dermis, dentin</td>
<td>Rare form</td>
</tr>
<tr>
<td>II</td>
<td>α1(II)</td>
<td>[α1(II)]₃</td>
<td>Cartilage, notochord, vitreous body, embryonic epithelia, retina</td>
<td>Major cartilage collagen; forms heterofibrils with Col IX + XI</td>
</tr>
<tr>
<td>III</td>
<td>α1(III)</td>
<td>[α1(III)]₃</td>
<td>Reticular fibers of most tissues (lung, liver, dermis, spleen, vessel wall, etc.)</td>
<td>Often in mixed fibrils with type I collagen; present in reticular and elastic tissues; cystine bridges in triple helix</td>
</tr>
<tr>
<td>V</td>
<td>α1(V)</td>
<td>[α1(V)]₃</td>
<td>In vitro: hamster lung cell cultures lung, cornea, bone, fetal membranes; together with Col I</td>
<td>Propeptide partially retained in the fibrils; forms hetero-fibrils with type I collagen controls fibril diameter</td>
</tr>
<tr>
<td></td>
<td>α2(V)</td>
<td>[α1(V)]₂ α3(V)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>α3(V)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XI</td>
<td>α1(XI)</td>
<td>[α1(XI) α2(XI)]</td>
<td>Cartilage, vitreous body</td>
<td>Homologous to Col V; nucleates and controls cartilage collagen; fibril formation; α3(XI) same gene as for α1(II)</td>
</tr>
<tr>
<td></td>
<td>α2(XI)</td>
<td>α3(XI)</td>
<td>Bone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>α3(XI)</td>
<td>[α1(XI)]₂ α2(V)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XXIV</td>
<td>α1(XXIV)</td>
<td>n.d.</td>
<td>Bone, eye</td>
<td>Similar to type V collagen, contains TSP motif in N-propeptide</td>
</tr>
<tr>
<td>XXVII</td>
<td>α1(XXVII)</td>
<td>n.d.</td>
<td>Cartilage; eye and ear</td>
<td>Col27a1 gene 156 kb, 61 exons</td>
</tr>
<tr>
<td>Collagen Type</td>
<td>α1 Members</td>
<td>α1 Repeats</td>
<td>Tissue Expression</td>
<td>Structure/Function</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
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<td>-------------------</td>
</tr>
<tr>
<td>VI</td>
<td>α1(VI) α2(VI) α3(VI)</td>
<td>[α1(VI) α2(VI) α3(VI)]</td>
<td>Widespread, in cartilage (pericellular), intervert, disk dermis, placenta, lung vessel wall</td>
<td>Contains vWF and Kunitz type protein inhibitor domains; forms beaded filaments; highly disulfide crosslinked</td>
</tr>
<tr>
<td>X</td>
<td>α1(X)</td>
<td>[α1(X)]&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Hypertrophic cartilage</td>
<td></td>
</tr>
<tr>
<td>IX</td>
<td>α1(IX) α2(IX) α3(IX)</td>
<td>[α1(IX) α2(IX) α3(IX)]</td>
<td>Cartilage, vitreous humor Splice variant without NC-4 domain in cornea</td>
<td>Covalently linked to type II collagen fibrils; NC4 domain projects into cartilage matrix; contains chondroitin sulfate</td>
</tr>
<tr>
<td>XII</td>
<td>α1(XII)</td>
<td>[α1(XII)]&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Perichondrium, ligaments, tendon</td>
<td>Large cruciform shaped NC3 domain; associated with type I collagen fibrils</td>
</tr>
<tr>
<td>XIV</td>
<td>α1(XIV)</td>
<td>[α1(XIV)]&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Cartilage, dermis, tendon, vessel wall, placenta, lung, liver</td>
<td>Associated with type I collagen</td>
</tr>
<tr>
<td>XVI</td>
<td>α1(XVI)</td>
<td>[α1(XVI)]&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Cartilage (territorial matrix) papillary dermis</td>
<td>Integrates into discrete Col II/XI fibrils</td>
</tr>
<tr>
<td>XX</td>
<td>α1(XX)</td>
<td></td>
<td>Cornea; sternal cartilage</td>
<td>Less FN III repeats than Col XIV</td>
</tr>
<tr>
<td>XXI</td>
<td>α1(XXI)</td>
<td></td>
<td>Blood vessel wall</td>
<td>TSP and vWFA domain, but no FNIII rep.</td>
</tr>
<tr>
<td>XXII</td>
<td>α1(XXII)</td>
<td></td>
<td>Myotendinous junction, articular cartilage surface</td>
<td>Present only in tissue junctions</td>
</tr>
</tbody>
</table>
What is Marfan syndrome

• The condition is named after a French pediatrician, Antoine Marfan, who in 1896 described a 5-year-old girl whose arms, legs, fingers and toes were disproportionately long, muscle development was poor, and spine curved abnormally.
PARTS OF THE BODY AFFECTED BY MARFAN SYNDROME

EYESIGHT
near-sighted (myopic)
eye (or ocular) lens dislocation
retinal detachment

LUNGS
spontaneous lung collapse (pneumothorax)

CARDIO-VASCULAR SYSTEM
aorta widening or dilatation
aortic aneurysms
mitral and/or aortic valve(s) prolapse / leakage

SKELETON
curvature of the spine (scoliosis)
pigeon or funnel chest (pectus deformity)
tall stature
loose jointedness
Marfan Syndrome is an autosomal dominant disease. Because of this, a person who has this disease has a 50% chance of passing it on to their children.
Diagnosis

• Although the gene for the Marfan syndrome has been found, there is no simple blood test or skin biopsy to make the diagnosis.

• The diagnosis needs to be made after examinations by a number of doctors.

• By used “Ghent Criteria,” to decide if someone has Marfan syndrome (hard to diagnose named after the city in Belgium where doctors decided which features to include on the list.)
To correct diagnosis of Marfan Syndrome

• If no one else in the family has Marfan syndrome, then doctors diagnose Marfan syndrome when a person has major criteria in at least two body systems and a minor criteria in a third.

• If a parent or sibling (brother or sister) has Marfan syndrome, then doctors diagnose Marfan syndrome when a person has a major criteria in one body system and a minor criteria in another.
Pathogenesis

• Marfan syndrome is caused by mutations in the *FBN1* gene on chromosome 15, which encodes a glycoprotein called fibrillin-1, a component of the extracellular matrix. The Fibrillin 1 protein is essential for the proper formation of the extracellular matrix including the biogenesis and maintenance of elastic fibers. The extracellular matrix is critical for both the structural integrity of connective tissue but also serves as a reservoir for growth factors. Elastin fibers are found throughout the body but are particularly abundant in the aorta, ligaments and the ciliary zonules of the eye; consequently, these areas are among the worst affected
Role of transforming growth factor

- (TGFβ) plays an important role in Marfan syndrome. Fibrillin-1 indirectly binds a latent form of TGFβ keeping it sequestered and unable to exert its biological activity. The simplest model of Marfan syndrome suggests that reduced levels of fibrillin-1 allow TGFβ levels to rise due to inadequate sequestration. Although it is not proven how elevated TGFβ levels are responsible for the specific pathology seen with the disease, an inflammatory reaction releasing proteases that slowly degrade the elastin fibers and other components of the extracellular matrix is known to occur.
Treatment options

• A cure does not exist; but advances in medical and surgical treatments can improve life span
Treatments

• Regular checkups by a cardiologist are needed to monitor the health of the heart valves and the aorta. The goal of treatment is to slow the progression of aortic dilation and damage to heart valves by eliminating arrhythmias, minimizing the heart rate, and minimizing blood pressure. Beta blockers have been used to control arrhythmias and slow the heart rate.
Treatments

• Research in laboratory mice has suggested that the angiotensin II receptor antagonist losartan, which appears to block TGF-beta activity, can slow or halt the formation of aortic aneurysms in Marfan syndrome
Ehlers-Danlos syndrome (EDS)

- also known as "Cutis hyperelastica" is a group of inherited connective tissue disorders, caused by a defect in the synthesis of collagen (a protein in connective tissue). The collagen in connective tissue helps tissues to resist deformation (decreases its elasticity). In the skin, muscles, ligaments, blood vessels, and visceral organs collagen plays a very significant role and with increased elasticity, secondary to abnormal collagen, pathology results. Depending on the individual mutation, the severity of the syndrome can vary from mild to life-threatening.
Symptoms

Highly flexible fingers and toes
Loose, unstable joints that are prone to: sprains, dislocation, subluxations (partial dislocations), hyperextension (double jointedness) Flat feet
High and narrow palate, a sign, resulting in dental crowding
Easy bruising  Fragile blood vessels resulting from cystic medial necrosis with tendency towards aneurysm (even abdominal aortic aneurysm)
Velvety-smooth skin which may be stretchy
Abnormal wound healing and scar formation  Low muscle tone and Muscle weakness
Early onset of osteoarthritis
Cardiac effects:
Fibromyalgia symptoms: (chronic conditions characterised by widespread pain in your muscles, ligaments and tendons as well as fatigue and multiple tender points.)
Other, less common signs and complications may include: Osteopenia (low bone density) (club foot ), especially in the Vascular type
Deformities of the spine, such as:
Functional bowel disorders (functional gastritis, irritable bowel syndrome)
Vascular skin conditions:
## Types of EDS

<table>
<thead>
<tr>
<th>Types</th>
<th>Description</th>
<th>COL 5 A1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 3</td>
<td>Affects 1 in 10,000 to 15,000 and is caused by an autosomal dominant or autosomal recessive mechanism. Mutations in either of two separate genes (which are also involved in Vascular EDS) Extreme flexibility is the hallmark of this type.</td>
<td>COL3 A1</td>
</tr>
<tr>
<td>Types 1 &amp; 2</td>
<td>Deficiency of type I and type V collagen Affects approximately 2 to 5 in 100,000 people. It is caused by autosomal dominant mechanism</td>
<td>COL 5 A1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>COL 5 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>COL 1A1</td>
</tr>
<tr>
<td>Type</td>
<td>Description</td>
<td>COL3 A1</td>
</tr>
<tr>
<td>------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Type 4</td>
<td>Is an autosomal dominant defect in the type-III collagen synthesis; affecting approximately 1 in 100,000 to 250,000 people. The vascular type is considered one of the more serious forms of Ehlers-Danlos syndrome because blood vessels and organs are more prone to tearing (rupture)</td>
<td></td>
</tr>
<tr>
<td>Type 6</td>
<td>Is an autosomal dominant defect due to deficiency of lysyl hydroxylase it is very rare, with fewer than 60 cases reported. The kyphoscoliosis type is characterised by progressive curvature of the spine (scoliosis), fragile eyes, and severe muscle weakness</td>
<td>PLOD1</td>
</tr>
<tr>
<td>Type 7 A&amp; B</td>
<td>Is also very rare, with about 30 cases reported. It affects type-I collagen. The arthrochalasia type is characterised by very loose joints and dislocations involving both hips.</td>
<td>COL1A1, COL1A2</td>
</tr>
<tr>
<td>Type 7 C</td>
<td>very rare, with about 10 cases reported. The dermatosparaxis type is characterised by extremely fragile and sagging skin</td>
<td>ADAMTS2</td>
</tr>
</tbody>
</table>
Genetics

• Mutation in the following protein causes EDS
  1. Fibrous proteins: COL1A1, COL1A2, COL3A1, COL5A1, COL5A2,

  2. Enzymes:
     a. Metallopeptidases (extracellular processing of procollagen to tropocollagen. (ADAM TS2)
     b. Lysylhydroxylase (PLOD1)
ADAMTS2 Gene

- EDS dermatosparaxis type is caused by mutations in the ADAMTS2 gene. Several mutations in the ADAMTS2 gene have been identified in people with this syndrome. These mutations greatly reduce the production of the enzyme made by the ADAMTS2 gene. Procollagen cannot be processed correctly without this enzyme. As a result, collagen fibrils are not assembled properly; they appear ribbon-like and disorganized under the microscope. Cross-links, or chemical interactions, between collagen fibrils are also affected. These defects weaken connective tissue (the tissue that binds and supports the body's muscles, ligaments, organs, and skin), which causes the signs and symptoms of the disorder.
Lysyl hydroxylase

• **Lysyl hydroxylase (or procollagen-lysine 5-dioxygenase)** is an oxygenase enzyme which catalyzes the hydroxylation of lysine to hydroxylysine. This reaction is necessary to the formation and stabilization of collagen. It takes place following protein synthesis (as a post-translational modification). The protein is a membrane-bound homodimeric enzyme that is localized to the cisternae (lumen) of the rough endoplasmic reticulum.

• It requires iron and vitamin C as cofactors.
Treatment of EDS

• Symptomatic treatment
• Use of Vitamin C can help bruising and injuries.
• Exercise that strengthens muscles can support the joints.
Sticklers syndrome

- **Stickler syndrome** is a group of genetic disorders affecting connective tissue, specifically collagen. It was first studied and characterized by Gunnar B. Stickler in 1965. Stickler syndrome is a subtype of collagenopathy, types II and XI. Stickler syndrome is characterized by distinctive facial abnormalities, eye problems, hearing loss, and joint problems.
Types of Sticklers syndrome

Genetic changes are related to the following types of Stickler syndrome:

1. Stickler syndrome Type I, COL11A1 (chromosome 12q13)
2. Stickler syndrome Type II, COL11A2 (chromosome 1p21)
3. Stickler syndrome Type III, COL2A1 (chromosome 6p21.3)
4. Sticklers syndrome Type IV COL9A1 (chromosome 6q13)
Biosynthesis of Collagen and Elastin
Blood vessels

Collagen I synthesis

Collagenolysis

Cross-linking to stabilize

Mechanically Strong and Compliant Vessel

Elastin synthesis

Elastolysis

Cross-linking to stabilize
Genetic Testing

- COL2A1 → 27-80% mutations found
- COL11A1 → 50-80%
- COL11A2 → unknown but available
- COL9A1 → unknown and unavailable

But the mutation in these genes are associated with a number of other diseases.
Sticklers syndrome type I

• Type II Collagen ➔ made up of three chains of collagen encoded by COL2A1
  – Causes Stickler Syndrome Type 1
  – The most common type Type II collagen, which adds structure and strength to connective tissues, is found primarily in cartilage, the jelly-like substance that fills the eyeball (the vitreous), the inner ear, and the centre portion of the discs between the vertebrae in the spine (nucleus pulposus). Three pro-alpha1(II) chains twist together to form a triple-stranded, rope-like procollagen molecule.
Type XI Collagen

- Type XI Collagen is made up of three different strands encoded by:
  - COL2A1
  - COL11A1
  - COL11A2

- Mutations in COL11A1 cause Stickler Syndrome type II
- COL11A2 causes non ocular Stickler Syndrome or Stickler Syndrome Type III
Col11 A1 Gene location The COL11A1 gene is located on the short (p) arm of chromosome 1 at position 21.
Genotype and phenotype

- Mutations in COL11A1 have typical Stickler eye findings—usually a beaded pattern vitreopathy (rarely membranous)
  “alpha 1 chain”

- COL11A2 not expressed in vitreous (COL5A2 chain replaces it in Type XI Collagen) → therefore no eye problems in Type II Stickler with COL11A2 mutations
  “alpha 2 chain”
Collagen type IX

• Type IX Collagen composed of one strand each encoded by three different genes:
  – COL9A1
  – COL9A2
  – COL9A3

  – Mutations in COL9A1 can cause autosomal recessive Stickler Syndrome– Type IV
Putting all the genetics together

<table>
<thead>
<tr>
<th>Stickler-type</th>
<th>Collagen defect</th>
<th>Genes making 3 strands in this collagen</th>
<th>mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Type II</td>
<td>COL2A1</td>
<td>COL2A1</td>
</tr>
<tr>
<td>II</td>
<td>Type XI</td>
<td>COL2A1, COL11A1, COL11A2</td>
<td>COL11A1</td>
</tr>
<tr>
<td>III non ocular</td>
<td>Type XI</td>
<td>COL2A1, COL11A1, COL11A2</td>
<td>COL11A2</td>
</tr>
<tr>
<td>“IV” (recessive)</td>
<td>Type IX</td>
<td>COL9A1, COL9A2, COL9A3</td>
<td>COL9A1</td>
</tr>
</tbody>
</table>
Genetics of Sticklers syndrome

The syndrome is thought to arise from a mutation of several collagen genes during fetal development. It is a sex independent autosomal dominant trait meaning a person with the syndrome has a 50% chance of passing it on to each child. There are three variants of Stickler syndrome identified, each associated with a collagen biosynthesis gene. A metabolic defect concerning the hyaluronic acid and the collagen of the 2-d type is assumed to be the cause of this syndrome.
Stickler Syndrome (type IV) due to COL9A1: autosomal recessive

Both parents carry one gene mutation but do not have Stickler → 25% probability of each child having Stickler Syndrome

Child who inherits mutated gene from both mother and father have Stickler Syndrome →
Stickler Syndrome gene locations

- COL11A1
- COL11A2
- COL9A1 + COL9A1
- COL2A1
Stickler Syndrome gene locations

COL11A1

COL11A2

COL9A1

COL2A1
Symptoms

- A characteristic feature of Stickler syndrome is a somewhat flattened facial appearance. This is caused by underdeveloped bones in the middle of the face, including the cheekbones and the bridge of the nose.

- A particular group of physical features, called the Pierre Robin syndrome, is common in children with Stickler syndrome.

- Robin sequence includes a U-shaped or sometimes V-shaped cleft palate (an opening in the roof of the mouth, with a tongue that is too large for the space formed by the small lower jaw. Children with a cleft palate are also prone to frequent ear infections and swallowing difficulties.
Symptoms

• Near sightedness
• People with sticklers syndrome eye are more prone to increased pressure within the eye resulting in Glaucoma,
• Early onset of Arthritis
• Hearing loss
• Learning difficulties can also occur because of hearing and sight impairments.
Treatments

Systematic treatments can improve or correct many of the symptoms of this disorder. For example

1. Use of glasses or contact lenses.
2. Hearing aids can help the people with hearing problems.
3. Children with Stickler syndrome and/or Pierre-Robin sequence (PRS) may need a feeding evaluation palate or jaw surgery, orthodontics, or speech therapy.
4. full-body x-ray to correct the bone and joint problem