Heritable Disorders of ConnectiveTissue

Chapter 425 | Part 12: Endocrinology and Metabolism

KEY CLINICAL POINTS

1. Fibrodysplasia ossificans progressiva (FOP) is caused by an activating mutation in activin receptor A type 1, leading to ectopic bone formation.
2. Osteogenesis imperfecta (OI) is characterized by bone fragility, deformity, and blue sclerae; pulmonary disease is the leading cause of death.
3. Tumoral calcinosis results from mutations in GALNT3, FGF23, or α-Klotho, causing spontaneous soft tissue calcification.
4. Collagen biosynthesis requires a Gly-X-Y repeating sequence; defects in prolyl 4-hydroxylase (P4H1) lead to scurvy.
5. Palovarotene is approved for FOP (females >8, males >10) to reduce new heterotopic ossification.
6. Surgical removal of ectopic bone in FOP is contraindicated as trauma may trigger further bone formation.
7. Type I collagen is the primary protein in dermis, ligaments, tendons, and demineralized bone; Type II is predominant in cartilage.
8. Fibrillin mutations (e.g., FBN1) are central to Marfan syndrome and other thoracic aortic diseases.
9. Collagen types III, V, VII, IX, XI, XVII, and XXVII are associated with a wide range of specific connective tissue disorders.
10. Diagnosis involves matching clinical symptoms to established classifications before determining the necessity of DNA analysis.

DEFINITION & CLASSIFICATION

- **Definition (Harrison's 22e):** Heritable disorders of connective tissue are conditions transmitted genetically in families that produce clinically obvious changes in the bone, cartilage, skin, or relatively acellular tissues such as tendons.
- **Connective Tissue Composition:**
  - Complex interacting extracellular matrix (ECM) network.
  - Components: Collagens, proteoglycans, and numerous noncollagenous glycoproteins/proteins.
  - "The Matrix": Approximately 500 potential building blocks providing tissue-specific function.
- **Collagen Types & Distribution:**
  - Type I: Most abundant in dermis, ligaments, tendons, and demineralized bone.
  - Type II: Most abundant protein of cartilage.
  - Type III: Found in dermis, aorta, uterus, intestine; Type I and III are most abundant in large blood vessels.
- **Classification Challenges:**
  - Debate exists between classification by clinical presentation vs. causative genes.
  - 552 genes associated with 771 defined disorders of the skeleton.

– Current (2023) nosology uses a "hybrid" dyadic naming system (phenotypic entity + gene).

– Factors for grouping: Causal gene, shared radiographic features, or similar clinical course (e.g., lethality).

EPIDEMIOLOGY

- **Historical Context:**
  - – McKusick identified specificity of diseases for select tissues.
  - – Evolution from few known genes to hundreds of different genes in connective tissues.
- **Clinical Refinement:**
  - – Initial classifications (e.g., Ehlers-Danlos syndrome) were refined as more patients were examined.
  - – Recognition of genetic heterogeneity: Different phenotypes can arise from the same gene; same phenotype can result from different mutations.

ETIOLOGY & PATHOPHYSIOLOGY

- **Tissue Dynamics:**
  - – Connective tissues are not inert; they undergo synthesis, degradation, and resynthesis.
  - – Growth phases: Rapid turnover during embryonic development and puberty; slower but steady metabolism in adulthood (except bone).
  - – Degradation factors: Age, malnutrition, physical inactivity, low gravitational stress.
- **Collagen Biosynthesis Pathway:**

1. Synthesis of procollagen (soluble precursor with globular domains at ends) on ribosomes.
2. Entry into rough endoplasmic reticulum (ER) → removal of signal peptides.
3. Post-translational modifications:
   - – Hydroxylation: Proline and lysine in the Gly-X-Y triplet are hydroxylated by prolyl 4-hydroxylase (P4H1) and lysyl hydroxylase (LH1).
   - – Requirement: P4H1 requires ascorbic acid (Vitamin C) as a cofactor; deficiency leads to scurvy.
   - – Glycosylation: Lysine residues glycosylated with galactose or glucose.
4. Assembly: Proα chains form trimer nuclei → fold into triple helix in a zipper-like manner.
5. Transport & Secretion: Folded procollagen moves via COPII vesicles to Golgi → secreted into pericellular space.
6. Processing: Proteases remove N- and C-propeptides → reduces solubility 1000-fold → drives self-assembly into fibrils.
7. Cross-linking: Covalent bonds between α chains provide high tensile strength.

- **Structural Components:**
  - – Minor Collagens: Type V (with Type I) and Type XI (with Type II) modulate fibril assembly/morphology.
  - – SLRPs: Small leucine-rich proteins influence fiber organization.
  - – Elastin & Fibrillin: Fibrillins contain EGF-like domains and cysteine-rich domains; critical for TGF-β signaling.
  - – Proteoglycans: Provide resistance to compression (e.g., in cartilage or aorta).

CLINICAL FEATURES

- **Tumoral Calcinosis:**
  - Cause: Mutations in *GALNT3*, *FGF23*, or α-Klotho.
  - Presentation: Spontaneous soft tissue calcification; may occur with hyperphosphatemia (e.g., secondary hyperparathyroidism from hemodialysis, hypoparathyroidism).
- **Fibrodysplasia Ossificans Progressiva (FOP):**
  - Cause: Activating mutation in activin receptor A type 1.
  - Presentation: Ectopic bone formation in fascia, tendons, and ligaments.
- **Osteogenesis Imperfecta (OI):**
  - Cause: Mutations in *COL1A1* or *COL1A2*.
  - Features: Bone fragility, fractures, deformity, blue sclerae, dentinogenesis imperfecta, hearing loss.
  - Severity: Range from mildest end (osteoarthritis/osteoporosis) to severe syndromic forms.

DIFFERENTIAL DIAGNOSIS

- **Clinical Overlap:**
  - Some patients with skin changes similar to Ehlers-Danlos syndrome (EDS) may present with other features like extreme hypotonia or sudden rupture of large blood vessels.
  - Distinction between benign polymorphisms and pathogenic mutations in noncollagenous genes.

DIAGNOSTIC APPROACH

1. **Clinical Correlation:** Match patient signs/symptoms with established clinical classifications.
2. **Decision Point (DNA Analysis):** Determine if genetic testing is indicated based on:
   - Cost of analysis.
   - Rigor of the link between clinical phenotype and specific mutation.
   - Potential for reassurance to patients/families.
   - Utility for prenatal diagnosis.
   - Availability of mutation-specific therapies.

MANAGEMENT & TREATMENT

1. **Tumoral Calcinosis Treatment:**
   - Address underlying causes of hyperphosphatemia (e.g., secondary hyperparathyroidism, hypoparathyroidism).
2. **Fibrodysplasia Ossificans Progressiva (FOP) Management:**
   - Pharmacotherapy: Palovarotene (Approved 2023) for females >8 years and males >10 years to reduce new heterotopic ossification.
   - Surgical Caution: Do not perform surgical removal of ectopic bone → risk of trauma-induced formation of new heterotopic bone.
3. **Osteogenesis Imperrence (OI) Management:**
   - Pulmonary focus: Manage complications from repeated pneumonia, restrictive/obstructive disease, scoliosis, and chest wall deformity.

COMPLICATIONS & PROGNOSIS

- **Osteogenesis Imperfecta (OI):**
  - Primary cause of death: Pulmonary disease.
- **Fibrodysplasia Ossificans Progressiva (FOP):**
  - Risk of rapid progression of heterotopic bone following physical trauma/surgery.

KEY PEARLS & HIGH-YIELD POINTS

- **Scurvy Link:** P4H1 requires ascorbic acid; deficiency leads to underhydroxylated procollagen and failure of wound healing.
- **FOP Treatment:** Palovarotene is the specific approved agent for reducing new ossification.
- **Collagen Specificity:**
  - Type I: Bone, skin, tendons (OI, EDS).
  - Type III: Blood vessels (Vascular EDS, Alport).
  - Type V: Skin/Cartilage (Classic EDS).
- **Thoracic Aortic Disease:** Linked to mutations in *FBN1* (Marfan), *COL3A1* (Vascular EDS), and TGF-β signaling pathway genes (*TGFBR1*, *TGFBR2*, *SMAD3*, *TGFB2*, *TGFB3*).

TABLES

- **Table 425-1: Constituents of Connective Tissues and Associated Heritable Conditions**
  - Collagen I: Bone, cornea, dermis, tendon → OI (fractures, blue sclerae), EDS, Caffey disease.
  - Collagen III: Dermis, aorta, uterus, intestine → Vascular EDS; Basement membranes → Alport syndrome (*COL4A3/A4/A5*), Brain small-vessel disease (*COL4A1/A2*).
  - Collagen V: Placental tissue, bone, dermis, cornea → Classic EDS; Uterus, dermis, cornea, cartilage → Bethlem myopathy and Ullrich congenital muscular dystrophy.
  - Collagen VII: Skin, amniotic membrane, mucosal epithelium → Dystrophic epidermolysis bullosa; Descemet's membrane, endothelial cells → Corneal dystrophy.
  - Collagen IX: Cartilage, vitreous → Stickler syndrome (Spondyloepiphyseal dysplasia, high myopia); Calcifying cartilage → Multiple epiphyseal dysplasia.
  - Collagen XI: Cartilage, intervertebral disk → Various chondrodysplasias; Dermis, tendon, cartilage → Myopathic EDS.
  - Collagen XVII: Corneal epithelial cells → Junctional epidermolysis bullosa; Pia, blood vessels of developing human cerebral cortex → Knobloch syndrome.
  - Collagen XXVII: Chondrocytes, epithelial cell layers → Steel syndrome (Osteochondrodysplasia); Cartilage, tendon, ligament, bone → Pseudoachondroplasia, Multiple epiphyseal dysplasia.
  - Elastin: Dermis, arterial wall, lung → Cutis laxa, Marfan syndrome, Weill-Marchesani-syndrome, Stiff skin syndrome, Geleophysic dysplasia.
  - Fibrillin 2: Bruch membrane → Congenital contractural arachnodactyly (CCA/Beals-Hecht); Dermis, tendons, ligaments → Glomerulopathy with fibronectin deposits.
- **Table 425-4: Heritable Thoracic Aortic Disease and Associated Genes**
  - *COL3A1* → Vascular EDS.
  - *FBN1* → Marfan syndrome.
  - *MFAP5* → Familial thoracic aortic aneurysm 9.
  - *LOX* → Familial thoracic aortic aneurysm 10.
  - *TGFBR1/2*, *SMAD3*, *TGFB2/3* → Loeys-Dietz syndrome (1-5).

– *SMAD2* → Arterial aneurysms and dissections.
– *ACTA2* → Familial thoracic aortic aneurysm 6.
– *MYH11* → Familial thoracic aortic aneurysm 4.
– *MYLK* → Familial thoracic aortic aneurysm 7.
– *PRKG1* → Familial thoracic aortic aneurysm 8.

REFERENCE TABLES

TABLE 425-1
Constituents of Connective Tissues and Their Associated Heritable Conditions PROTEIN Collagen I

PROTEIN	TISSUE DISTRIBUTION	DISEASE	KEY MANIFESTATIONS
Collagen I	Bone, cornea, dermis, tendon	Osteogenesis imperfecta	Bone fragility with fractures and deformity; blue sclerae; dentinogenesis imperfecta; hearing loss
		EDS (various rare types)	Joint hypermobility; skin hyperextensibility; skin fragility; soft connective tissue fragility
		Caffey disease	Subperiosteal new bone formation; soft tissue swelling; fever and irritability
	Cartilage, vitreous	Various chondrodysplasias	
Collagen III	Dermis, aorta, uterus, intestine	Vascular EDS	Arterial, intestinal, and uterine fragility; thin translucent skin; easy bruising
	Basement membranes	Alport syndrome (COL4A3/A4/A5)	
		Brain small-vessel disease (COL4A1/A2)	
Collagen V	Placental tissue, bone, dermis, cornea	Classic EDS	Joint hypermobility; skin hyperextensibility; atrophic scarring
	Uterus, dermis, cornea, cartilage	Bethlem myopathy and Ullrich congenital muscular dystrophy	
Collagen VII	Skin, amniotic membrane, mucosal epithelium	Dystrophic epidermolysis bullosa	Skin blistering; oral and esophageal blistering; corneal erosions
	Descemet's membrane, endothelial cells	Corneal dystrophy	

PROTEIN	TISSUE DISTRIBUTION	DISEASE	KEY MANIFESTATIONS
Collagen IX	Cartilage, vitreous	Stickler syndrome	Spondyloepiphyseal dysplasia; early-onset osteoarthritis; high myopia; vitreoretinal abnormalities; hearing loss; cleft palate; midfacial hypoplasia
	Calcifying cartilage	Multiple epiphyseal dysplasia	
Collagen XI	Cartilage, intervertebral disk	Various chondrodysplasias	Skeletal dysplasia; ocular manifestations; hearing loss; orofacial findings
	Dermis, tendon, cartilage	Myopathic EDS	
Collagen XVII	Corneal epithelial cells	Junctional epidermolysis bullosa	Blistering of the skin and mucosae (mild to severe)
	Pia, blood vessels of the developing human cerebral cortex	Knobloch syndrome	
Collagen XXVII	Chondrocytes, epithelial cell layers in developing tissues, including stomach, lung, gonad, skin, cochlea, and tooth	Steel syndrome	Osteochondrodysplasia with hip dislocations; dislocations of radial heads; carpal coalition; short stature; facial dysmorphism; scoliosis
	Cartilage, tendon, ligament, bone	Pseudoachondroplasia	
		Multiple epiphyseal dysplasia	
Elastin	Dermis, arterial wall, lung	Cutis laxa	Wrinkled, redundant, sagging inelastic skin
		Williams syndrome	Cardiovascular disease (especially supravalvular aortic stenosis); orofacial features; intellectual deficit; connective tissue abnormalities; endocrine abnormalities
	Dermis, arterial wall, lung	Marfan syndrome	

PROTEIN	TISSUE DISTRIBUTION	DISEASE	KEY MANIFESTATIONS
		Weill-Marchesani-syndrome	
		Stiff skin syndrome	
		Geleophysic dysplasia	
Fibrillin 2	Bruch membrane	Congenital contractural arachnodactyly (CCA) or Beals-Hecht syndrome	Tall stature; arachnodactyly; (kypho)scoliosis; pectus deformities; contractures; muscle hypoplasia; mild cardiovascular involvement; long, narrow face, highly arched palate, micrognathia, crumpled external ears
		Acromelic dysplasia	Relative short stature; brachydactyly; toe walking; early onset carpal tunnel syndrome; short palpebral fissures
	Dermis, tendons, ligaments	Glomerulopathy with fibronectin deposits	
		Spondylometaphyseal dysplasia, corner fracture type	

TABLE 425-4

Heritable Thoracic Aortic Disease and Associated Genes and Proteins Extracellular matrix proteins

	GENE	PROTEIN	CONDITION	OMIM	LOCUS
Extracellular matrix proteins	COL3A1	α1(III) collagen chain	Vascular EDS	130050	2q32
	FBN1	Fibrillin 1	Marfan syndrome	154700	15q21.1
	MFAP5	Microfibrillar associated protein 5	Familial thoracic aortic aneurysm 9	616166	12p13.31
	LOX	Lysyl oxidase	Familial thoracic aortic aneurysm 10	617168	5q23.1

	GENE	PROTEIN	CONDITION	OMIM	LOCUS
	TGFBR1	Transforming growth factor receptor 1	Loeys-Dietz syndrome 1	609192	
	TGFBR2	Transforming growth factor receptor 2	Loeys-Dietz syndrome 2	610168	
	SMAD3	Mothers against deca pentaplegic drosophila homolog 3	Loeys-Dietz syndrome 3	613795	
	TGFB2	Transforming growth factor β2	Loeys-Dietz syndrome 4	614816	
	TGFB3	Transforming growth factor β3	Loeys-Dietz syndrome 5	615582	
	SMAD2	Mothers against deca pentaplegic drosophila homolog 2	Arterial aneurysms and dissections	/	
	ACTA2	Smooth muscle actin α2	Familial thoracic aortic aneurysm 6	611788	
Smooth muscle contraction	MYH11	Smooth muscle myosin heavy chain 11	Familial thoracic aortic aneurysm 4	132900	16p13.11
	MYLK	Myosin light chain kinase	Familial thoracic aortic aneurysm 7	613780	3q21.1
	PRKG1	Protein kinase cGMP -dependent type 1	Familial thoracic aortic aneurysm 8	615436	10q11.2-q21.1