

Marfan syndrome

Molecular pathogenesis · Morphology · Clinicopathologic correlation

Fibrillin-1

Extracellular microfibrils

TGF- β

Signaling dysregulation

Aorta

Life-threatening injury

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Learning objectives

- Explain FBN1-associated autosomal dominant disease
- Distinguish structural and signaling mechanisms
- Correlate the pathogenesis with organ-system findings
- Recognize why aortic assessment is central

Organize every manifestation around the underlying extracellular-matrix defect.

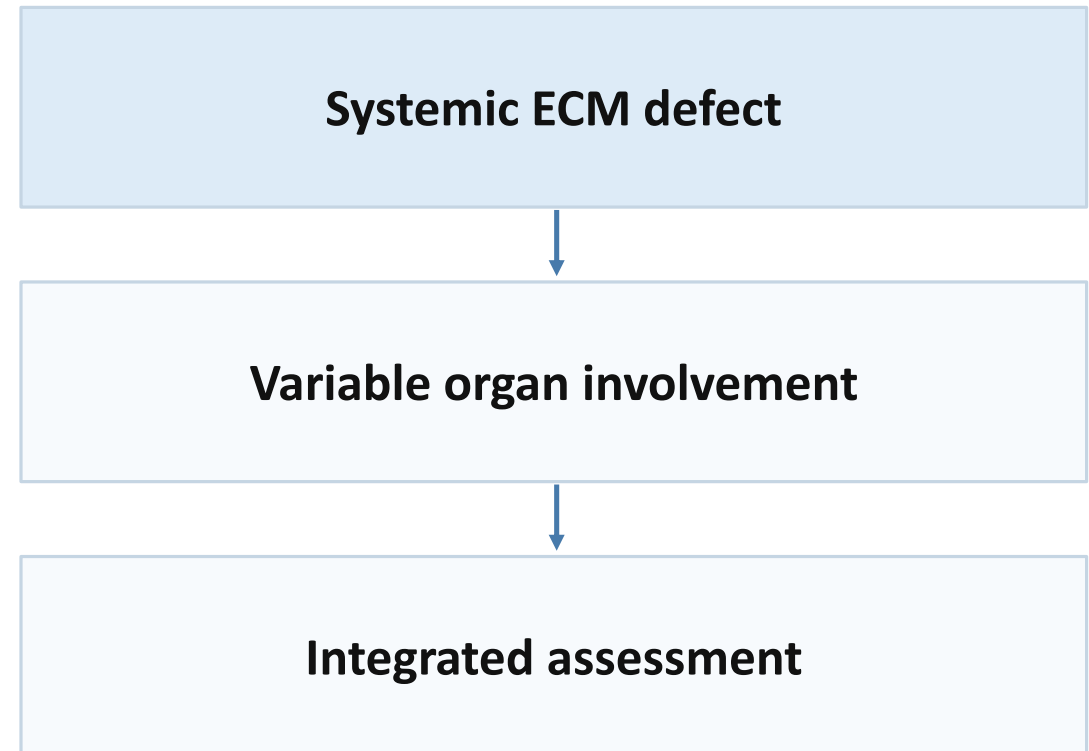
Marfan syndrome is a systemic connective-tissue disorder

Skeleton	Eyes	Cardiovascular
Growth and ligament findings	Lens-support abnormality	Aorta and cardiac valves

- The skeleton, eyes, and cardiovascular system are prominently affected
- A single molecular defect can produce disparate organ-level phenotypes
- Aortic disease determines much of the life-threatening risk

The multisystem pattern is more informative than body habitus alone

- Marked skeletal manifestations are not necessary in every affected patient
- Cardiovascular or ocular manifestations may predominate
- Clinical evaluation must not stop at tall stature



Schematic — causal sequence

Aortic disease carries the greatest clinical hazard

Feature	Clinical interpretation
Valve manifestations	Often detectable; may produce regurgitation
Aortic involvement	Threatens the integrity of the arterial wall

- Cardiac valve abnormalities may be frequent
- The aortic complications are more clinically consequential

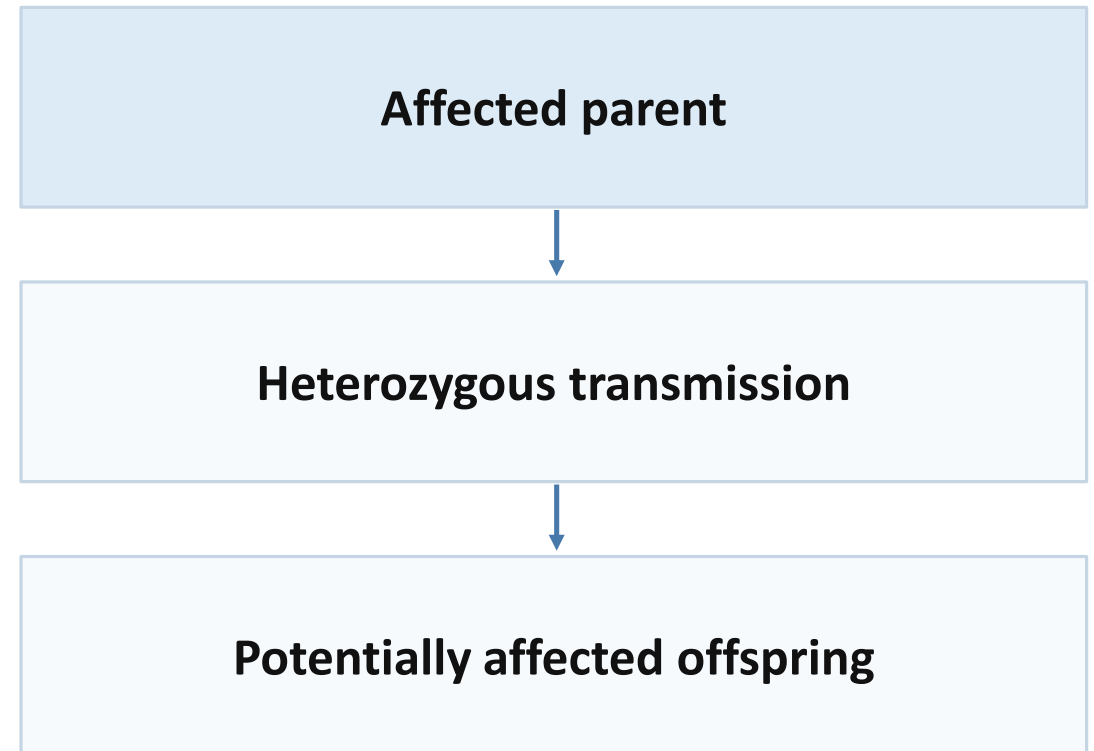
Prevalence is approximately 1 in 5,000

- This is the estimate reported by the source textbook
- The condition is uncommon yet important as a cause of inherited aortopathy
- The estimate describes population prevalence, not individual diagnostic probability

Epidemiologic prevalence cannot establish or exclude disease in an individual.

Most cases are familial

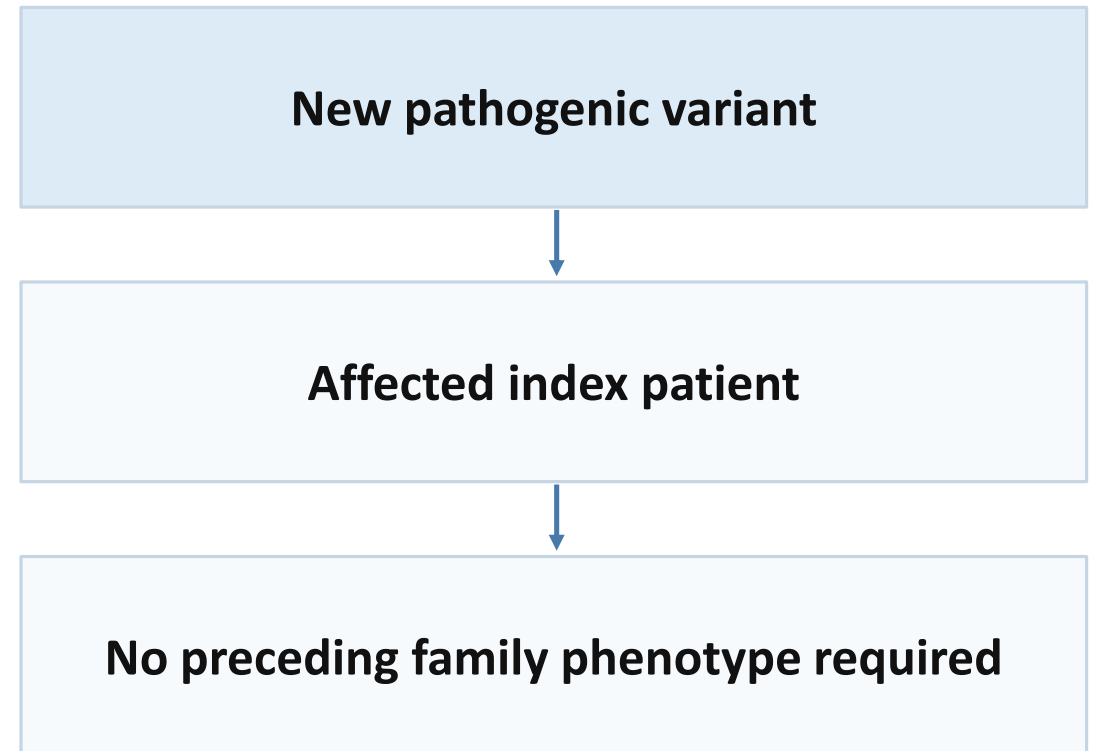
- Approximately 75% of cases are described as familial
- Marfan syndrome follows autosomal dominant inheritance
- Unaffected relatives do not exclude a de novo pathogenic variant



Schematic — causal sequence

De novo FBN1 variants account for sporadic presentations

- The source attributes the remaining cases to new mutations
- A negative reported family history is therefore not exclusionary
- A patient with no affected parent can still have an inherited structural-protein disorder



Schematic — causal sequence

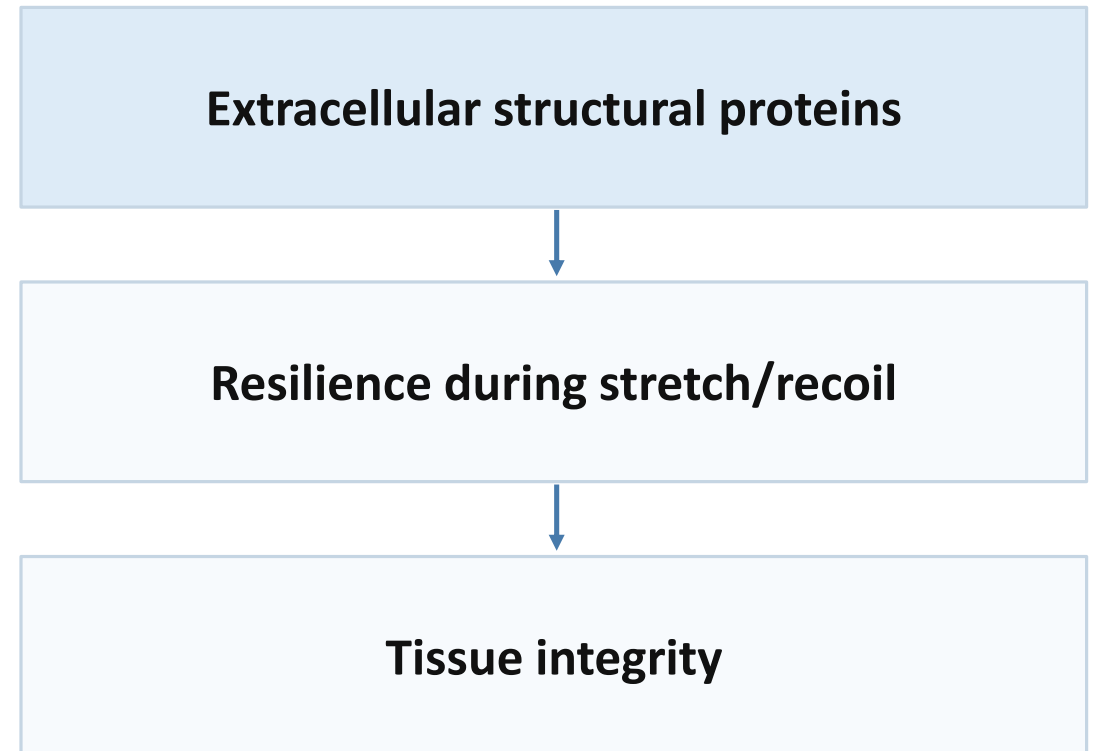
Autosomal dominant transmission affects both sexes

Family-history concept	Implication
Vertical transmission	Supports autosomal dominant inheritance
No affected parent	Compatible with a de novo variant
Affected heterozygote	50% transmission risk per pregnancy

- One heterozygous pathogenic variant can produce the phenotype
- Both males and females can be affected and transmit the variant

Connective tissue functions as an extracellular load-bearing system

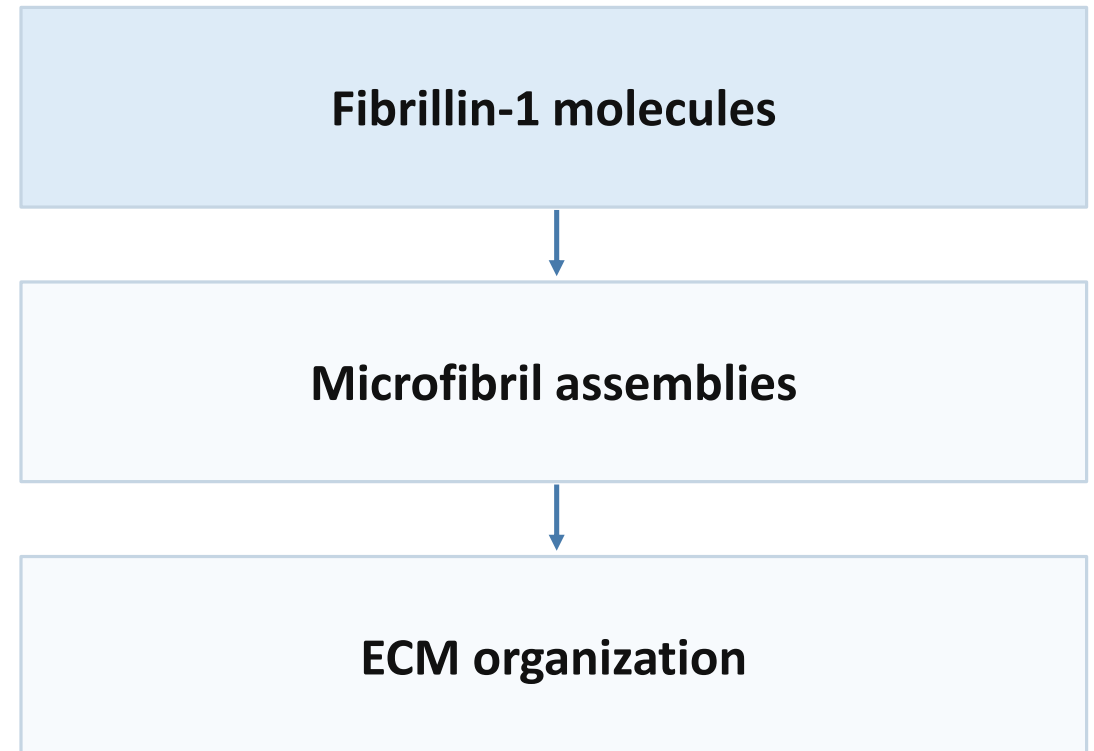
- Matrix proteins provide tensile support and resilience
- Tissues exposed to stretching and recoil depend on intact fiber networks
- A matrix defect may have both mechanical and signaling consequences



Schematic — causal sequence

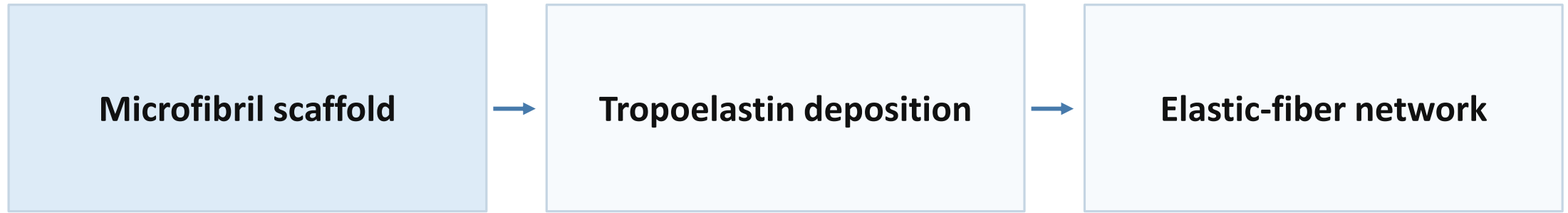
Fibrillin-1 is an extracellular microfibrillar glycoprotein

- Fibrillin-1 is a major constituent of matrix microfibrils
- Microfibrils form organized assemblies in connective tissues
- Abnormal fibrillin alters microfibril formation or abundance



Schematic — causal sequence

Microfibrils provide the scaffold for elastic fibers



- Microfibril bundles are laid down in the extracellular matrix
- Tropoelastin is deposited on that framework
- The resulting elastic-fiber architecture supports deformability and recoil

Schematic — stages or conceptual sequence

Elastic-fiber integrity matters most where tissues repeatedly stretch

Aorta	Ligaments	Zonules
Cyclic vessel-wall strain	Joint stabilization	Lens suspension

- The aorta is exposed to pulsatile mechanical stress
- Ligaments stabilize joints under movement
- Ciliary zonules suspend the crystalline lens

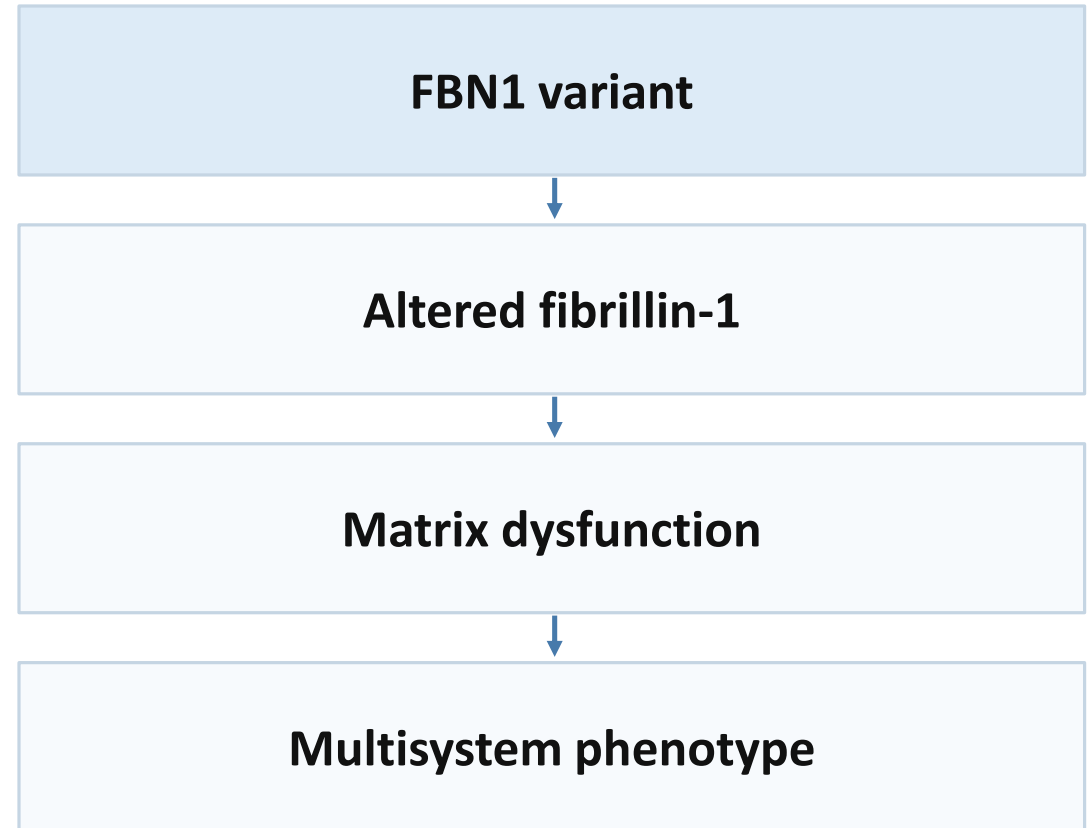
Fibrillin-1 and fibrillin-2 are distinct homologues

Gene	Protein	Source-linked disorder
FBN1	Fibrillin-1	Marfan syndrome
FBN2	Fibrillin-2	Congenital contractural arachnodactyly

- FBN1 encodes fibrillin-1 on chromosome 15q21.1
- FBN2 encodes fibrillin-2 on chromosome 5q23.31

FBN1 is the principal Marfan syndrome locus

- Mutations in FBN1 are associated with the classic disorder
- The encoded protein is part of the extracellular microfibril network
- Gene–protein–matrix–organ relationships provide a unifying explanation



Schematic — causal sequence

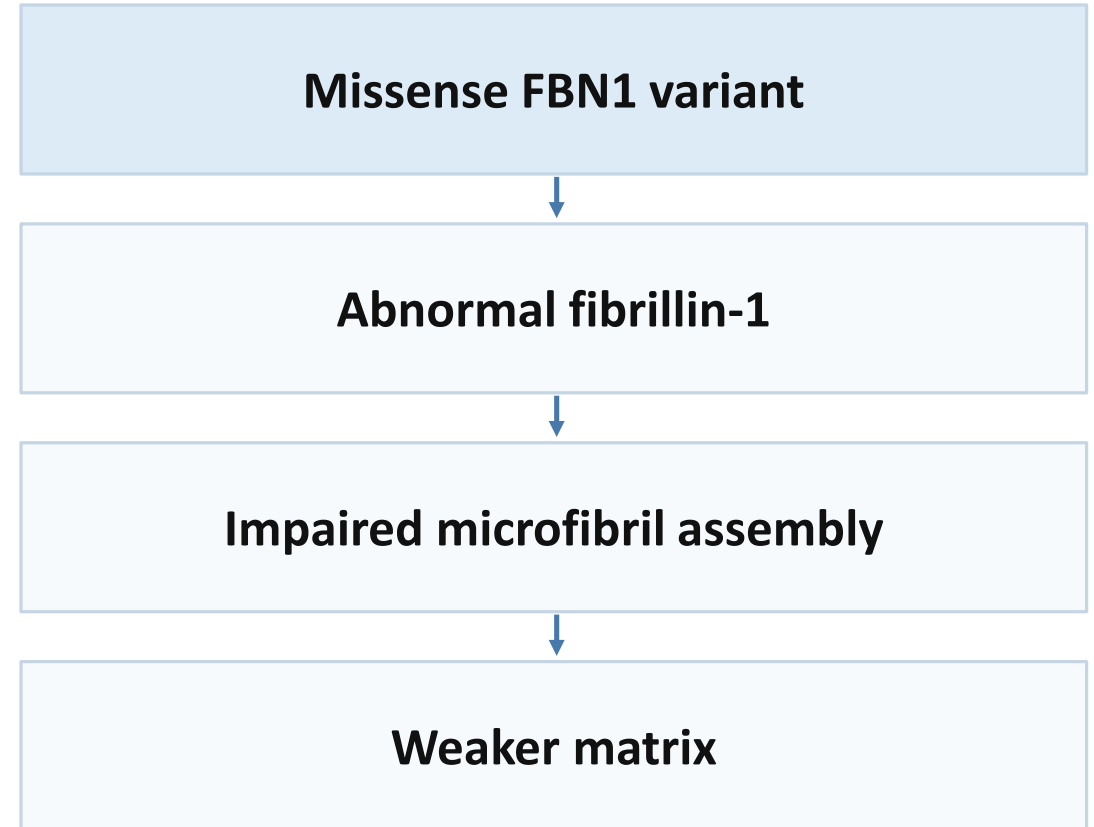
FBN1 variants are highly heterogeneous

- Close to 1,000 distinct identified mutations
- A single disorder arises from many different molecular alterations
- Sequence heterogeneity contributes to phenotypic heterogeneity

Do not equate a single named variant with the entire clinical syndrome.

Missense variants may exert dominant-negative effects

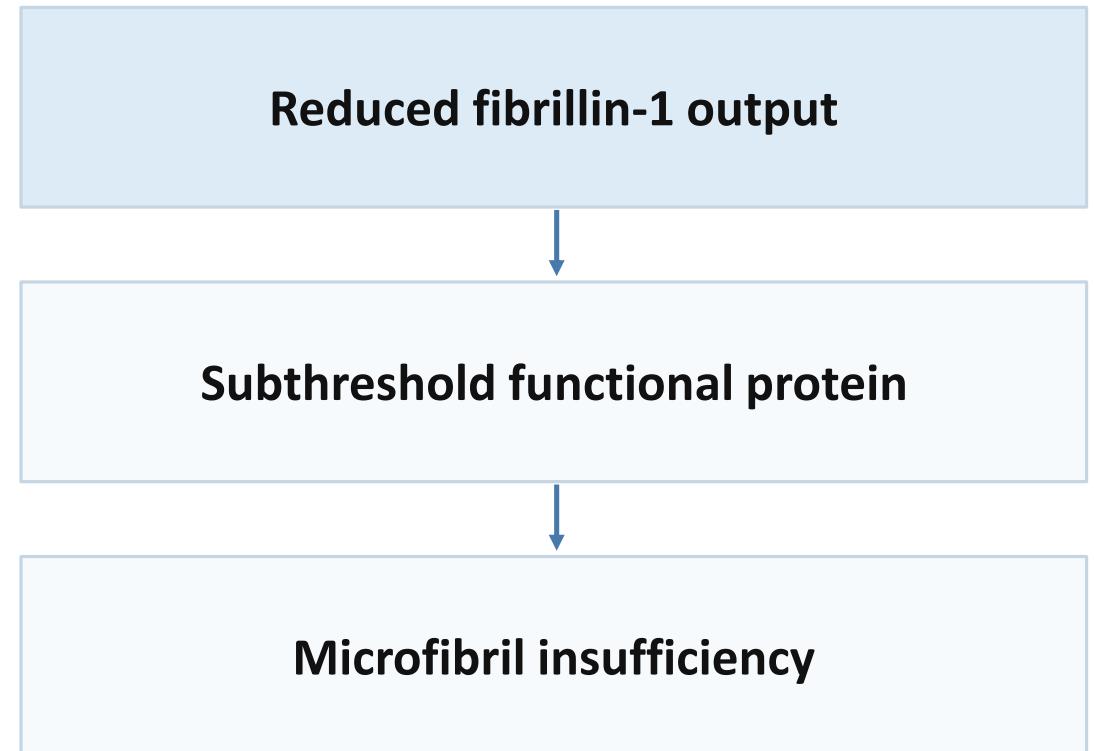
- Abnormal fibrillin-1 can disrupt fiber polymerization
- Mutant protein interferes with formation of a functional assembly
- One altered allele therefore compromises matrix structure



Schematic — causal sequence

Haploinsufficiency is a second mechanism

- Some variants reduce effective fibrillin-1 abundance
- The remaining allele does not supply sufficient functional protein
- The source assigns approximately 10–15% of cases to this category



Schematic — causal sequence

Dominant-negative and haploinsufficient defects differ

Feature	Dominant negative	Haploinsufficiency
Primary defect	Abnormal protein disrupts assembly	Insufficient functional protein
Common result	Compromised microfibrils	Compromised microfibrils

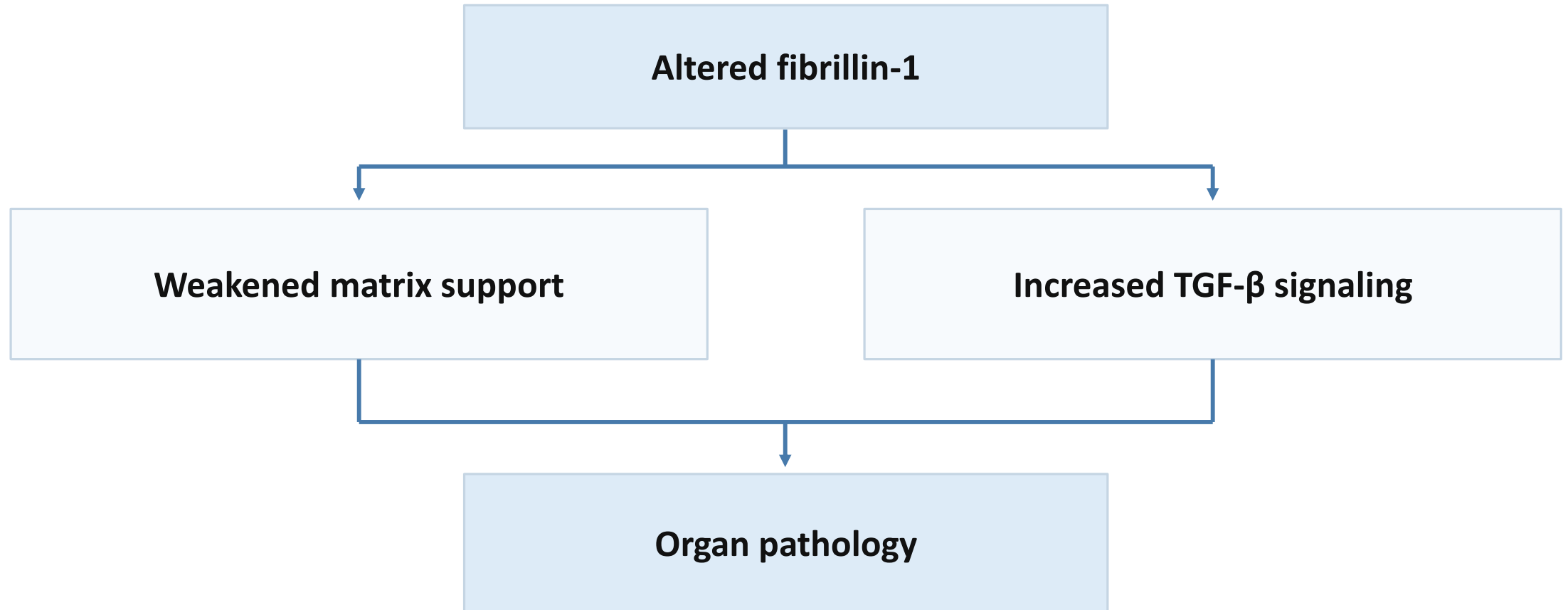
- Both converge on reduced effective extracellular support
- One mechanism disrupts assembly; The other lowers protein abundance

FBN2-related disease is a useful molecular contrast

- FBN2 variants are associated with congenital contractural arachnodactyly
- It is described as an autosomal dominant skeletal condition
- Similar fibrillin family membership does not imply identical phenotypes

The gene identity matters; Do not label every fibrillin-associated phenotype Marfan syndrome.

Marfan pathogenesis has two converging mechanisms

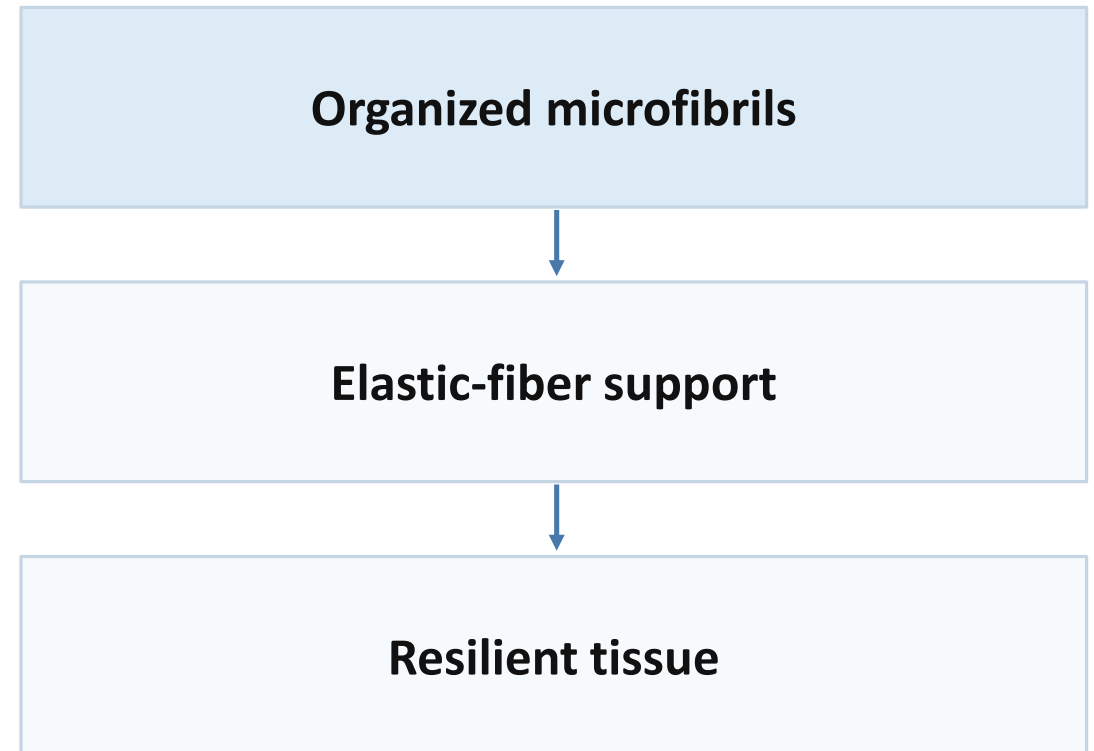


Loss of mechanical support in microfibril-rich matrix

Schematic — dual disease mechanisms

Normal microfibrils mechanically reinforce connective tissue

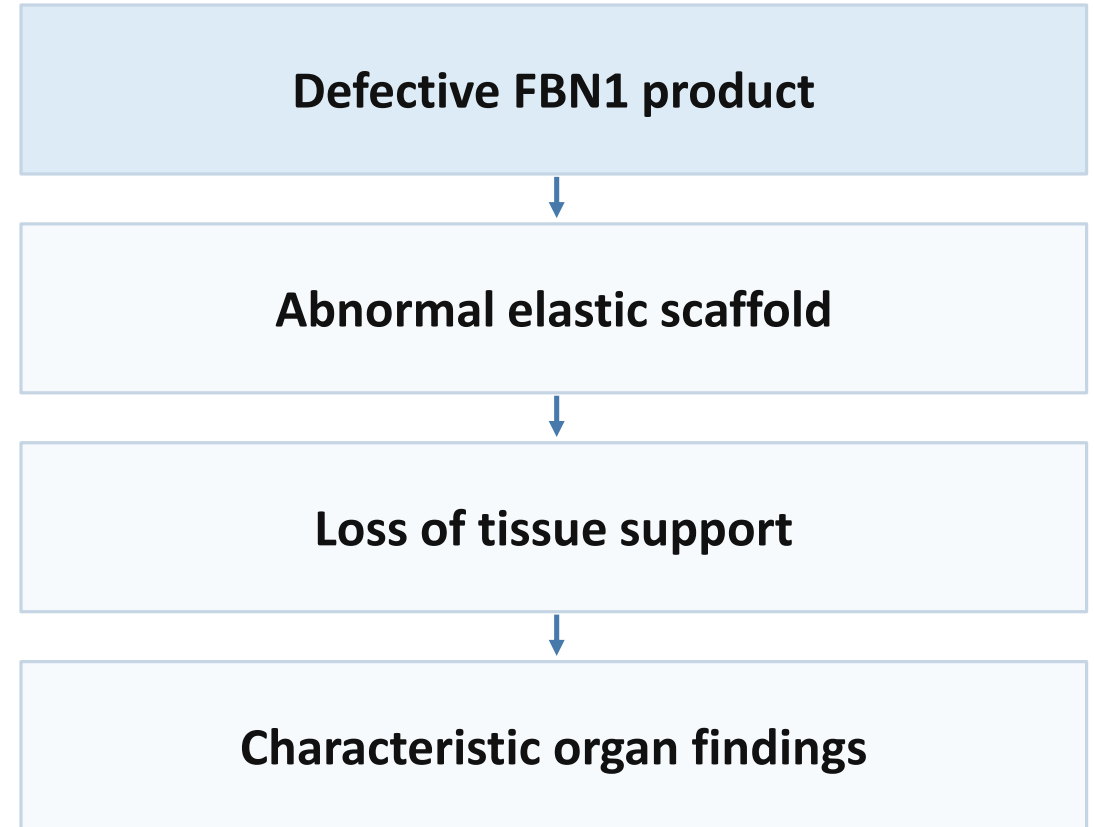
- Fibrillin-rich assemblies integrate with elastic-fiber architecture
- Elastic tissues withstand distortion and recover shape
- Organ integrity depends on the organized extracellular network



Schematic — causal sequence

Defective microfibrils weaken matrix-dependent tissues

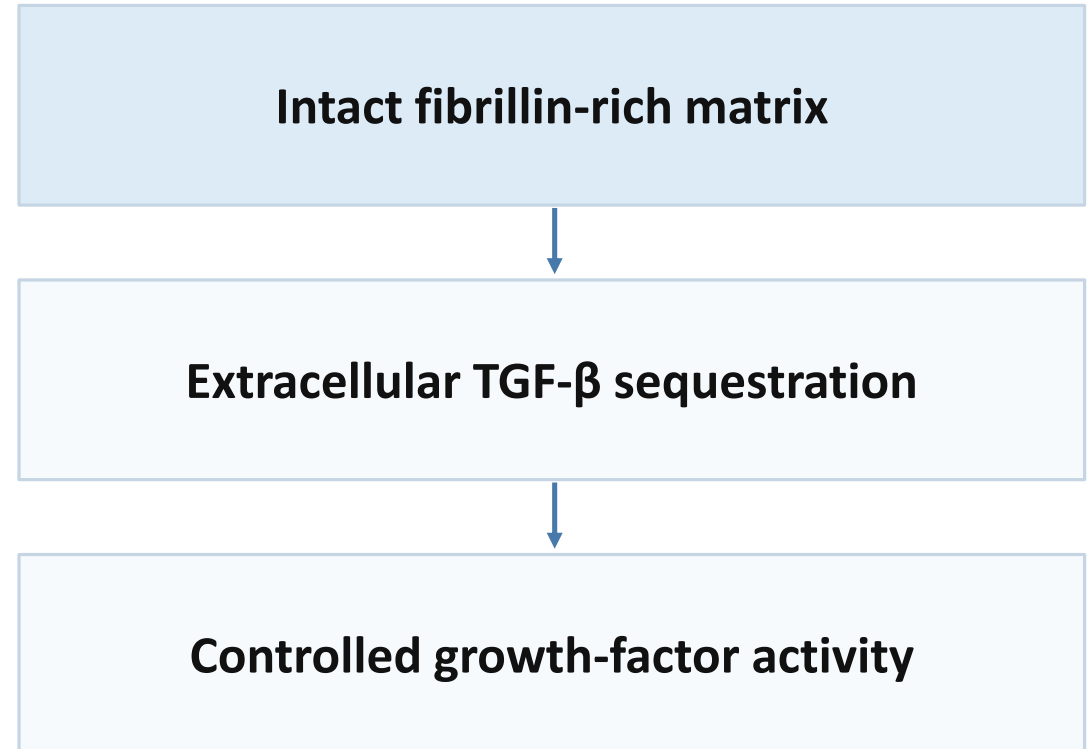
- Abnormal assembly disrupts the elastic-fiber framework
- The aorta, ligaments, and lens zonules are particularly susceptible
- Structural dysfunction explains several signature manifestations



Schematic — causal sequence

Microfibrils also regulate TGF- β availability

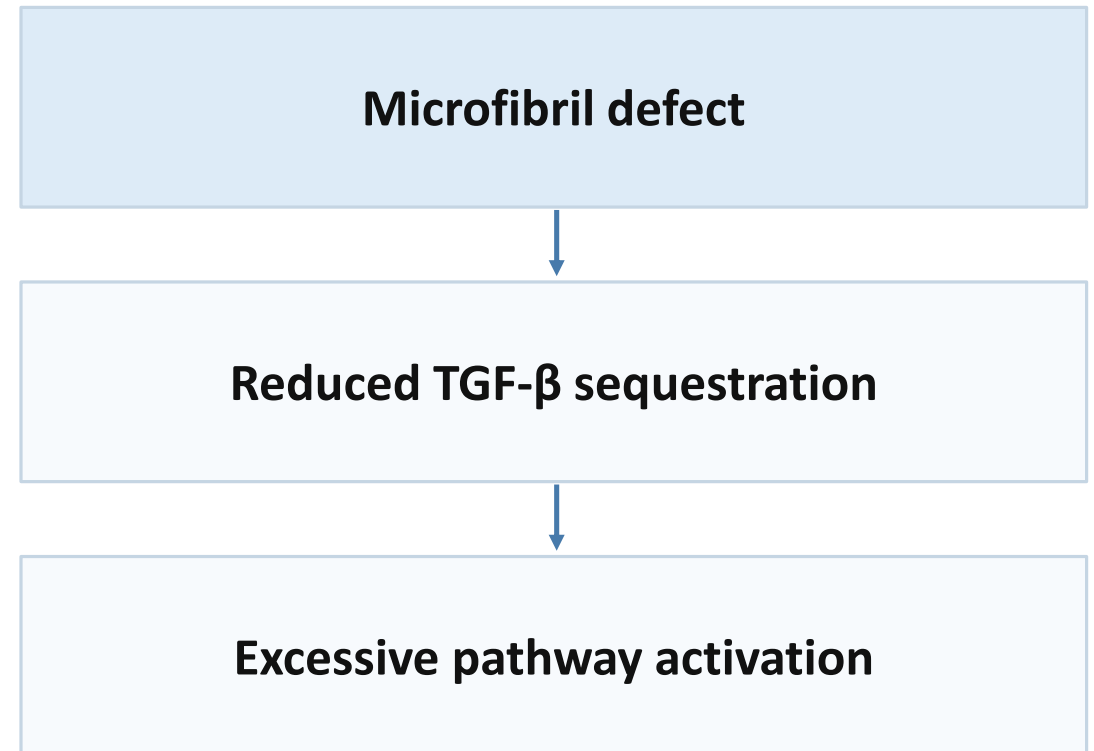
- Normal fibrillin-rich matrix sequesters TGF- β
- Extracellular sequestration limits signaling availability
- Microfibril dysfunction therefore perturbs growth-factor regulation



Schematic — causal sequence

Altered fibrillin can increase TGF- β signaling

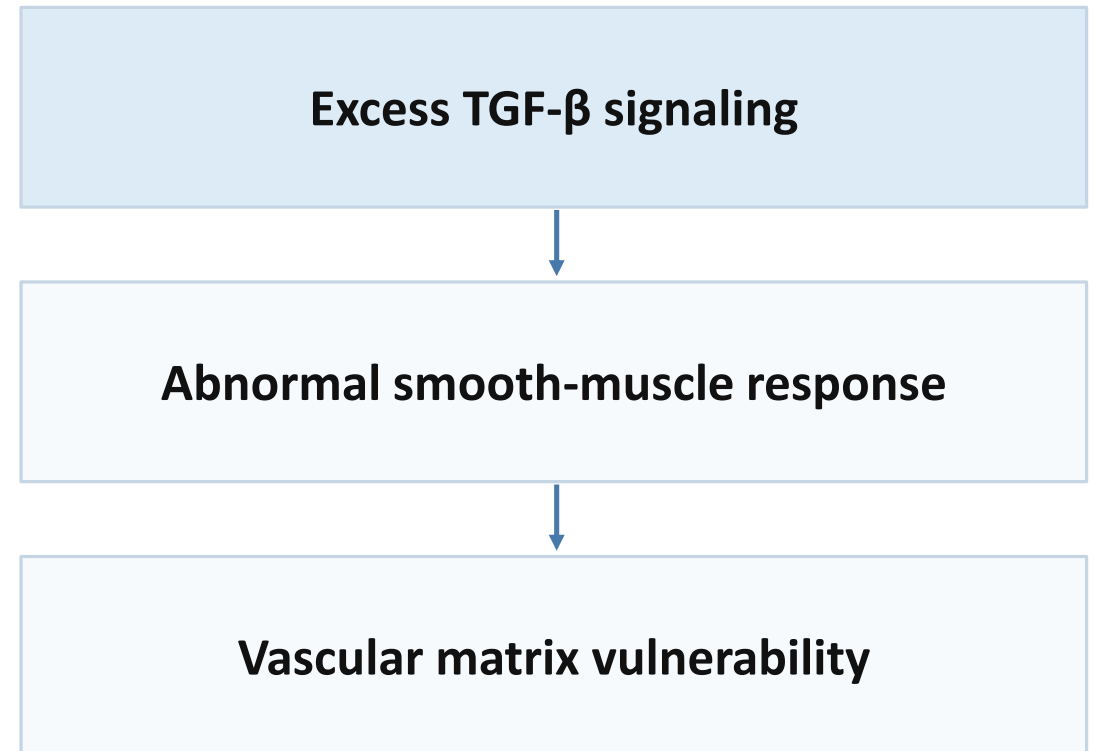
- Reduced or abnormal microfibrils impair sequestration
- More TGF- β becomes bioavailable to responsive cells
- Growth-factor dysregulation is a second disease mechanism



Schematic — causal sequence

Excessive TGF- β can disturb vascular smooth muscle biology

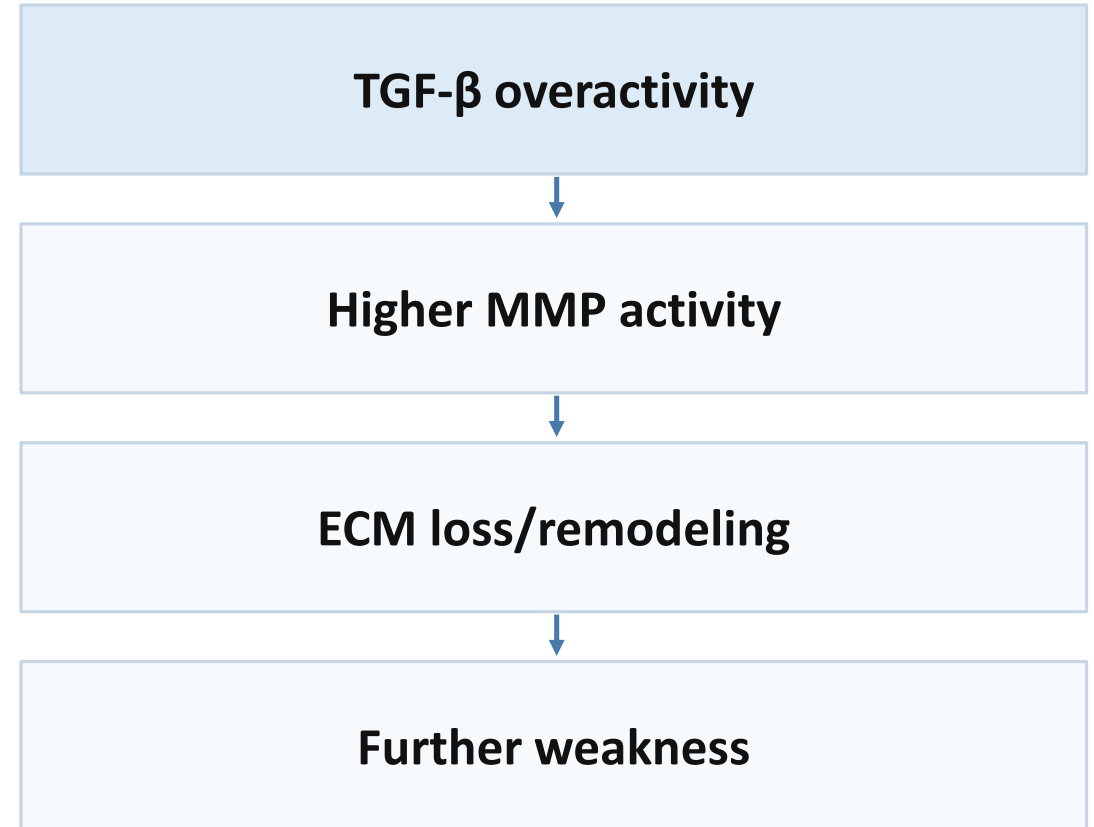
- The source links excess signaling to adverse smooth-muscle development
- Altered cell–matrix interactions may impair vascular-wall homeostasis
- This complements rather than replaces the structural explanation



Schematic — causal sequence

Matrix metalloproteinases promote extracellular degradation

- Excessive TGF- β signaling is linked to increased MMP activity
- MMPs degrade extracellular-matrix components
- Greater matrix turnover adds to structural weakness



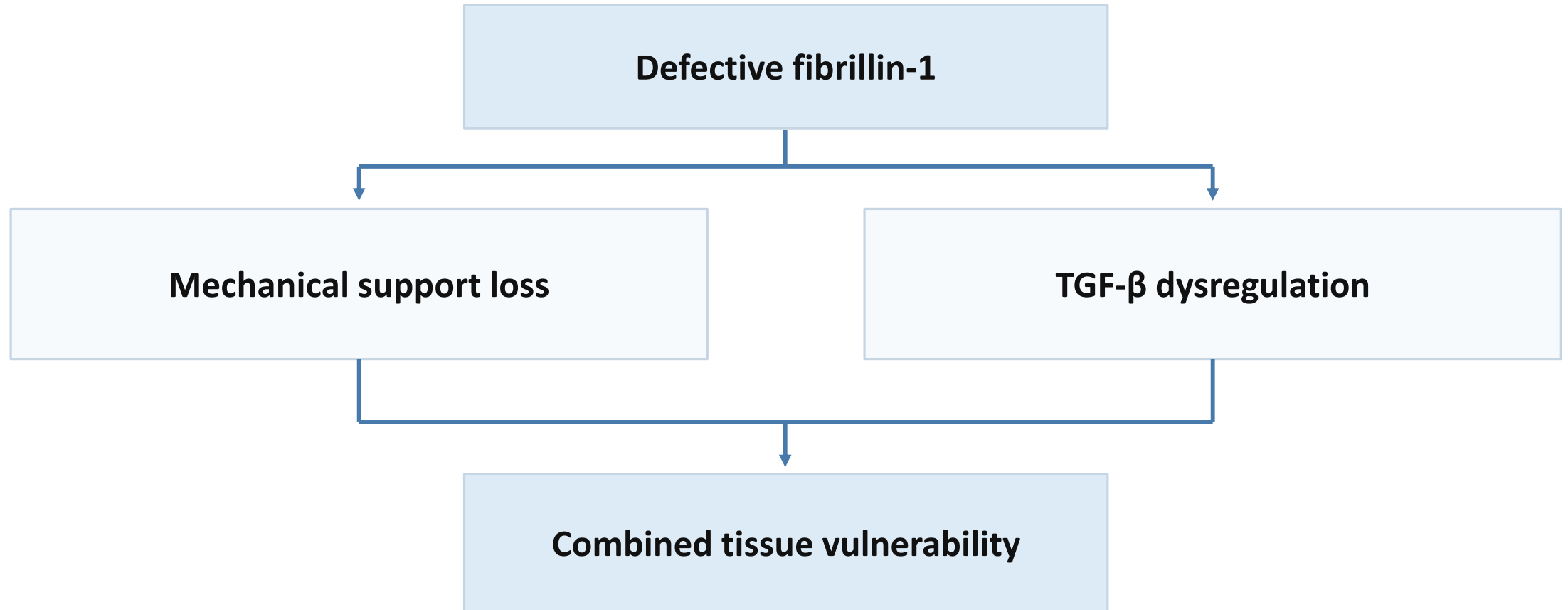
Schematic — causal sequence

TGF- β dysregulation explains features beyond reduced elasticity

Feature	Best emphasized pathway
Lens-zonule weakness	Structural support defect
Bone overgrowth	Signaling disturbance implicated
Myxoid valve change	Signaling disturbance implicated

- Matrix weakness alone does not readily explain all disease effects
- Bone overgrowth and myxoid mitral changes

The two pathways are complementary rather than competing



Mechanical effects weaken fibers and tissues

Schematic — dual disease mechanisms

Related TGF-pathway variants can resemble Marfan aortopathy

- The source describes disease associated with TGF- β type II receptor variants
- It also describes TGFB3-associated inherited aortic predisposition
- These observations support pathway involvement, not molecular identity with FBN1 disease

Distinct loci may converge on related aortic phenotypes; Preserve the genetic distinction.

A single defect produces variable manifestations

Mechanical demand	Signaling context	Molecular variant
Varies by organ	Varies by tissue	Varies by patient

- Different tissues depend on fibrillin-mediated support
- TGF- β biology differs across the skeleton, valves, and vasculature
- Mutation diversity contributes to variation among affected people

Phenotypic variability is clinically important

Presentation	Important limitation
Striking body habitus	Does not prove ocular disease
Dominant ocular phenotype	May have few skeletal signs
Dominant cardiac phenotype	May have few skeletal signs

- Some patients have striking skeletal changes
- Others present with predominantly ocular or cardiovascular disease

Skeletal manifestations are often the most visible

Body proportions	Joint and spine	Thorax
Long limbs and digits	Laxity and curvature	Anterior chest-wall deformity

- The source identifies skeletal abnormalities as striking features
- Typical findings concern height, proportions, joints, spine, and chest
- They should be interpreted as part of a multisystem pattern

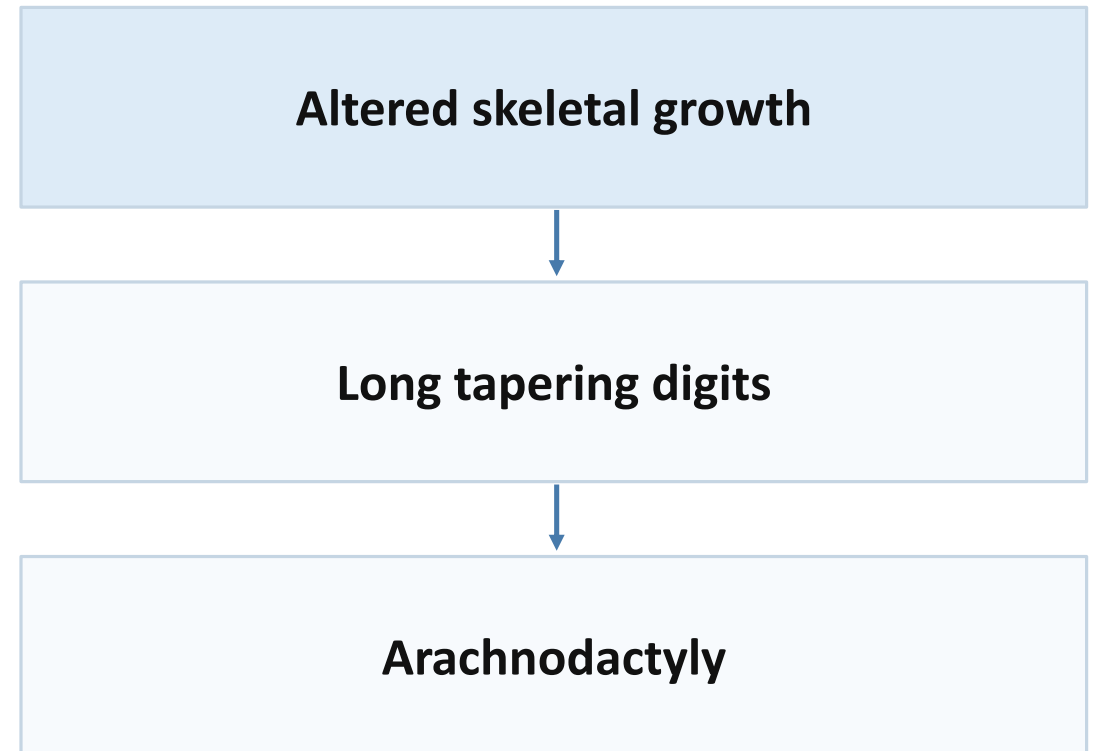
Excess longitudinal growth alters body proportions

- Many affected patients are unusually tall
- Extremities can be disproportionately long
- A tall body habitus is suggestive only in the right clinical context

Distinguish a characteristic habitus from a stand-alone diagnostic criterion.

Arachnodactyly describes long, tapering digits

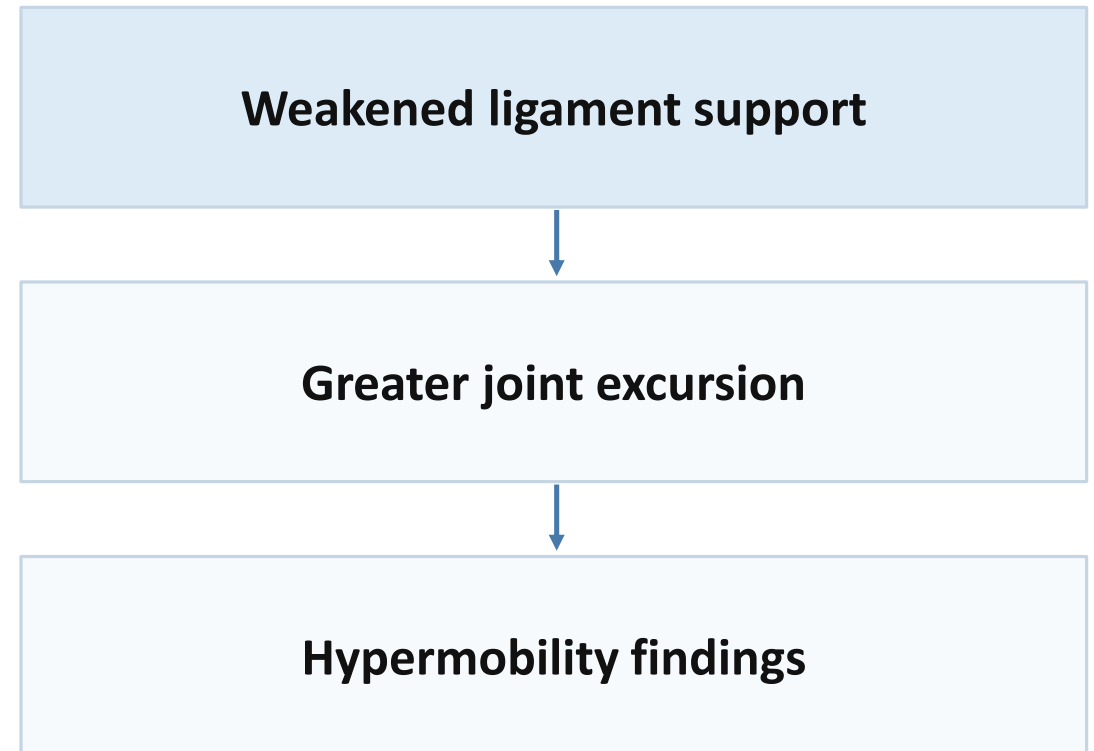
- Fingers and toes may be elongated and slender
- This is a morphological description, not a specific genotype
- Evaluate the finding alongside ocular and cardiovascular features



Schematic — causal sequence

Ligamentous laxity contributes to abnormal joint movement

- The source describes lax ligaments in hands and feet
- Some patients can hyperextend the thumb toward the wrist
- Excessive mobility reflects reduced connective-tissue restraint



Schematic — causal sequence

Craniofacial findings can support phenotype recognition

- The source describes dolichocephaly
- Frontal bossing and prominent supraorbital ridges are also described
- These features are supplementary, not equivalent to aortic assessment

Craniofacial appearance is nonspecific without the systemic context.

Spinal deformities reflect altered musculoskeletal support

Spinal change	Morphological description
Kyphosis	Excess sagittal curvature
Scoliosis	Lateral curvature
Rotational/slipping change	Altered vertebral alignment

- Kyphosis and scoliosis can occur
- Rotational or slipping changes of vertebrae are also described

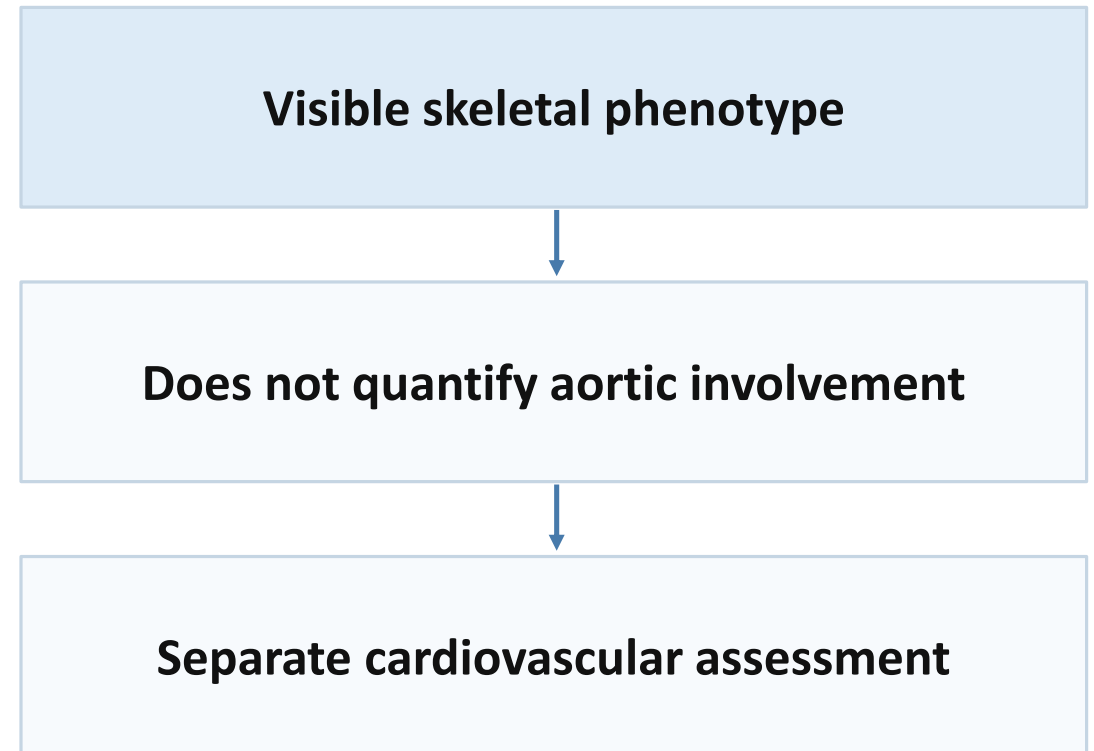
Chest-wall deformities are clinically recognizable

Deformity	Characteristic configuration
Pectus excavatum	Sunken anterior chest wall
Pectus carinatum	Protruding anterior chest wall

- Pectus excavatum is a depressed-sternum deformity
- Pectus carinatum produces anterior sternum prominence

Skeletal findings do not predict the severity of aortic disease

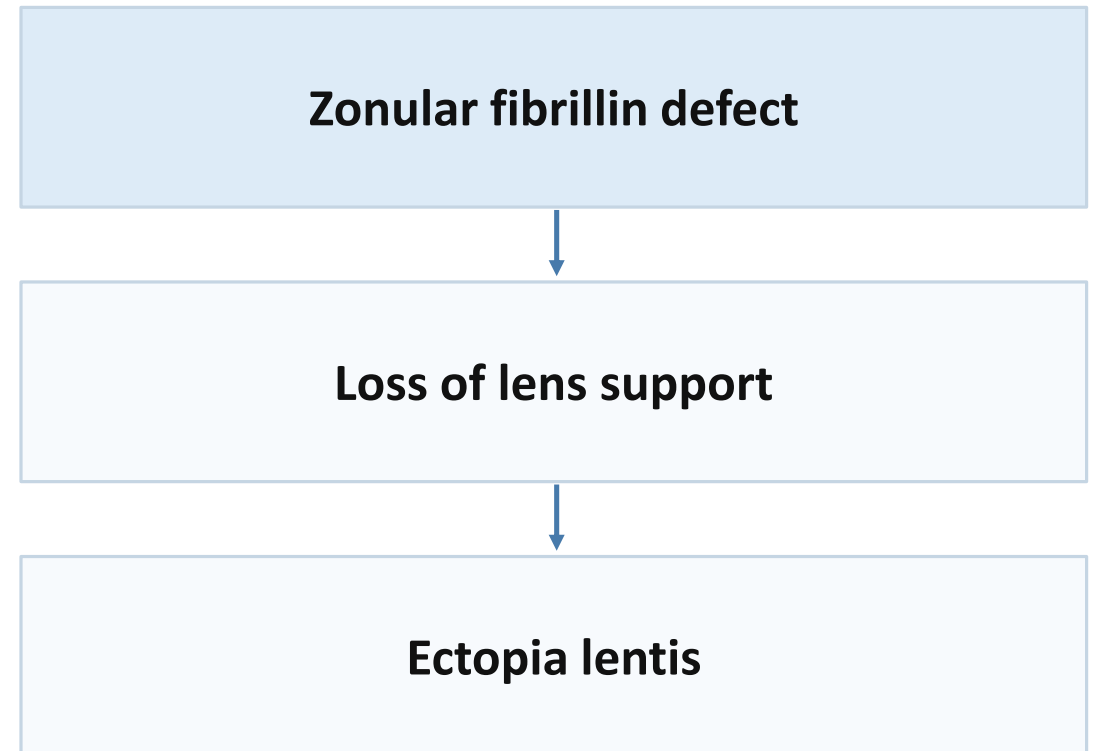
- Visible musculoskeletal changes may be extensive or subtle
- The source emphasizes marked interpatient clinical variability
- Cardiovascular assessment is necessary regardless of body habitus



Schematic — causal sequence

Zonular weakness causes ectopia lentis

- The lens is suspended by circumferential ciliary zonules
- Microfibrils are important for zonular tensile support
- Weakening predisposes to lens subluxation or dislocation



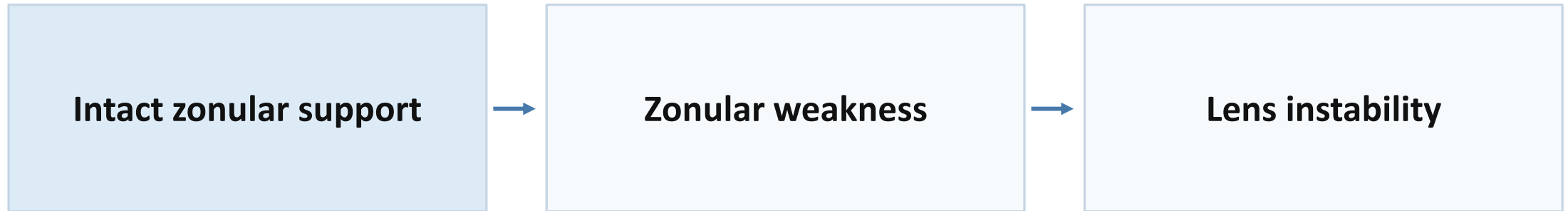
Schematic — causal sequence

Ectopia lentis is a particularly characteristic ocular finding

- Dislocation or subluxation can be bilateral
- Outward and upward displacement as typical
- Bilateral ectopia lentis should prompt consideration of Marfan syndrome

The diagnostic implication lies in the distinctive ocular–systemic association.

Lens displacement is a structural phenotype

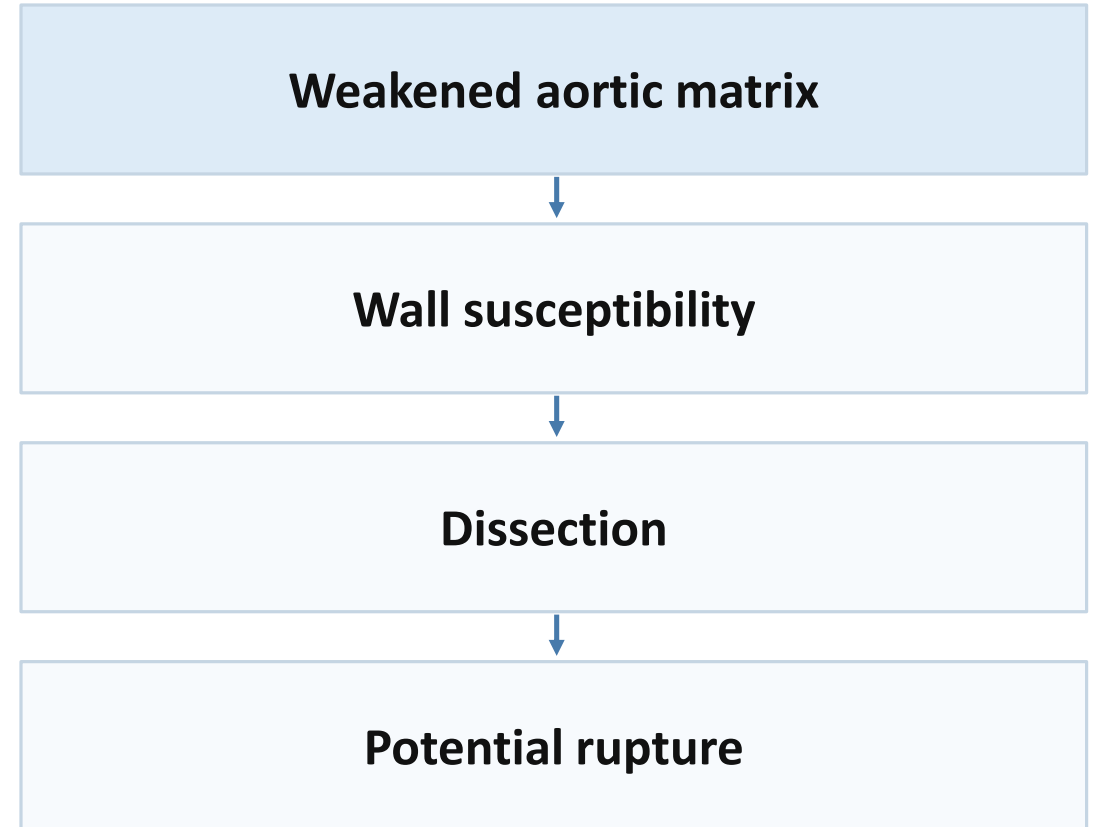


- Disrupted microfibrils weaken zonular attachments
- The resulting mechanical instability displaces the crystalline lens
- The ocular manifestation directly illustrates the support-defect pathway

Schematic — stages or conceptual sequence

Aortic involvement is the major life-threatening manifestation

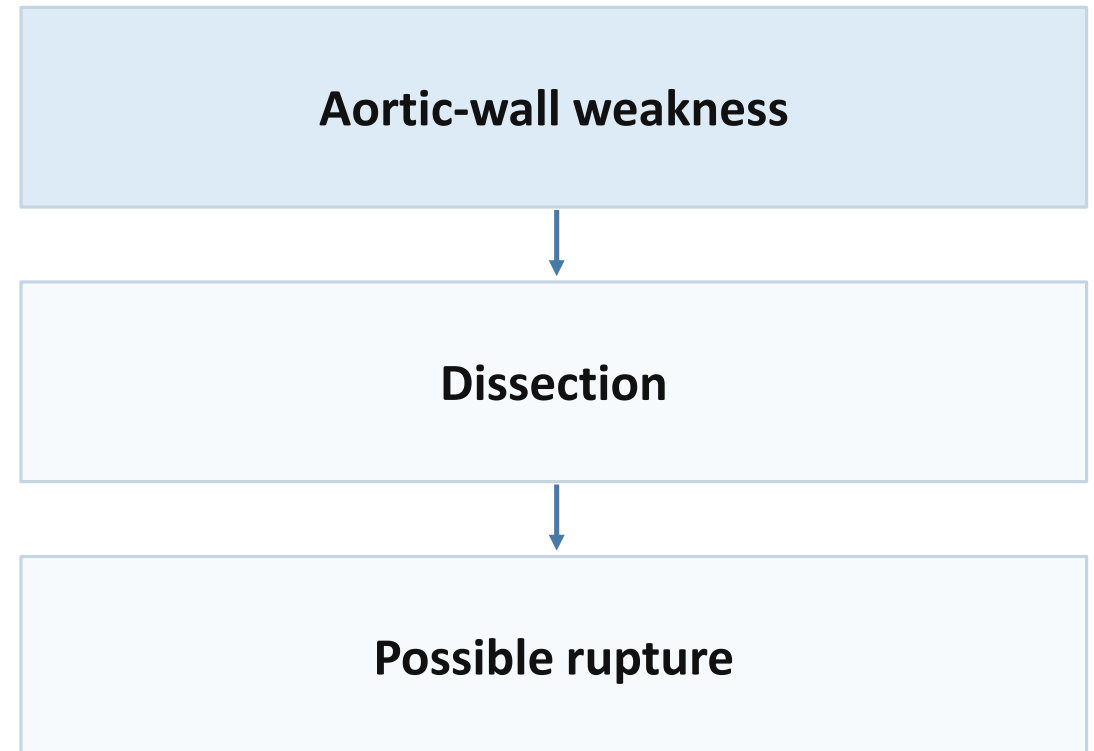
- The aortic wall relies on elastic-fiber integrity
- Extracellular-matrix dysregulation compromises vascular-wall resilience
- Aortic dissection and rupture are the major feared outcomes described



Schematic — causal sequence

Aortic dissection represents wall-layer separation

- The disease process involves compromised integrity of the aortic wall
- Dissection creates a dangerous separation within the wall
- Rupture of a dissection can cause catastrophic hemorrhage



Schematic — causal sequence

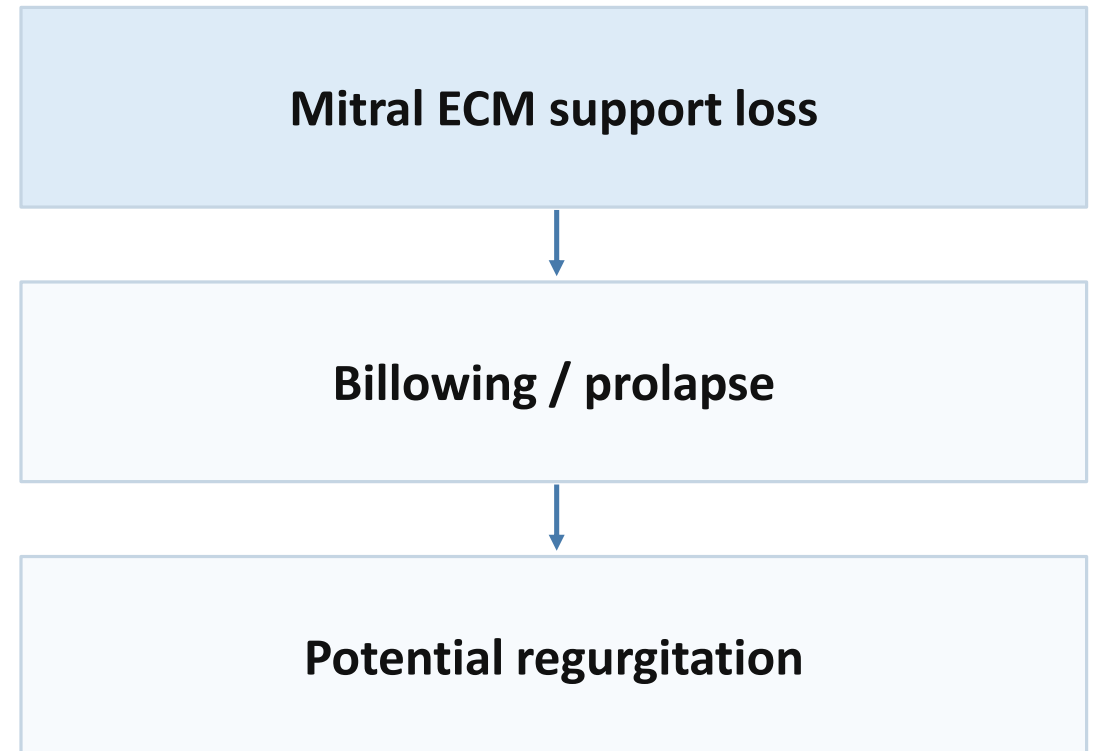
Clinical priority follows the consequences, not frequency alone

Issue	Mitral involvement	Aortic involvement
Dominant consequence	Regurgitant valve dysfunction	Dissection and possible rupture
Priority	Function and symptoms	Life-threatening structural risk

- Mitral lesions may be more frequent than some other abnormalities
- Aortic lesions carry greater threat to life

Loss of support makes mitral leaflets floppy

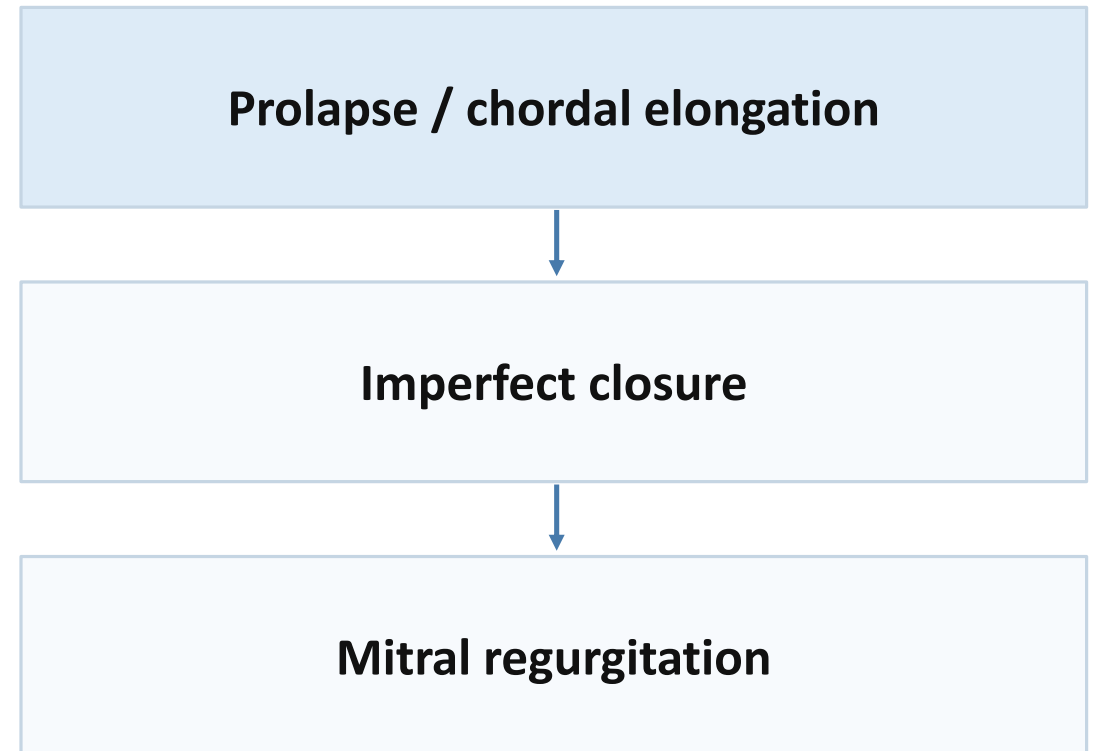
- Matrix weakness produces soft, billowy leaflets
- Mitral valve prolapse is a common cardiac finding
- Changes may be accompanied by elongated chordae tendineae



Schematic — causal sequence

Mitral valve prolapse may lead to regurgitation

- Abnormal leaflet movement interferes with normal closure
- Chordal lengthening can aggravate impaired coaptation
- Regurgitant flow is the major functional consequence described



Schematic — causal sequence

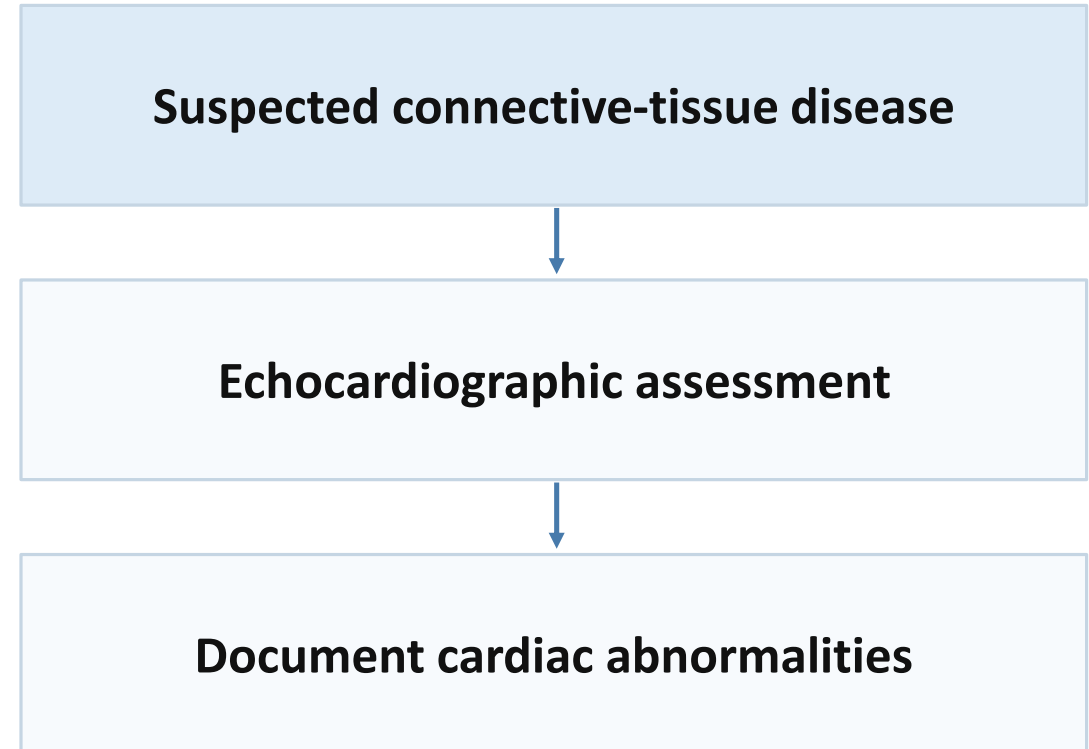
Other cardiac valves may also be affected

Mitral valve	Tricuspid valve	Aortic valve
Frequent prolapse/regurgitation	Similar changes possible	Similar changes less common

- The source reports similar changes in the tricuspid valve
- Aortic valve involvement is described as rarer
- Multivalvular findings reflect the systemic nature of matrix disease

Echocardiography identifies cardiovascular manifestations

- Its value in detecting cardiac abnormalities
- Valvular structure and function can be assessed
- Aortic and valve findings require direct evaluation rather than inference from appearance



Schematic — causal sequence

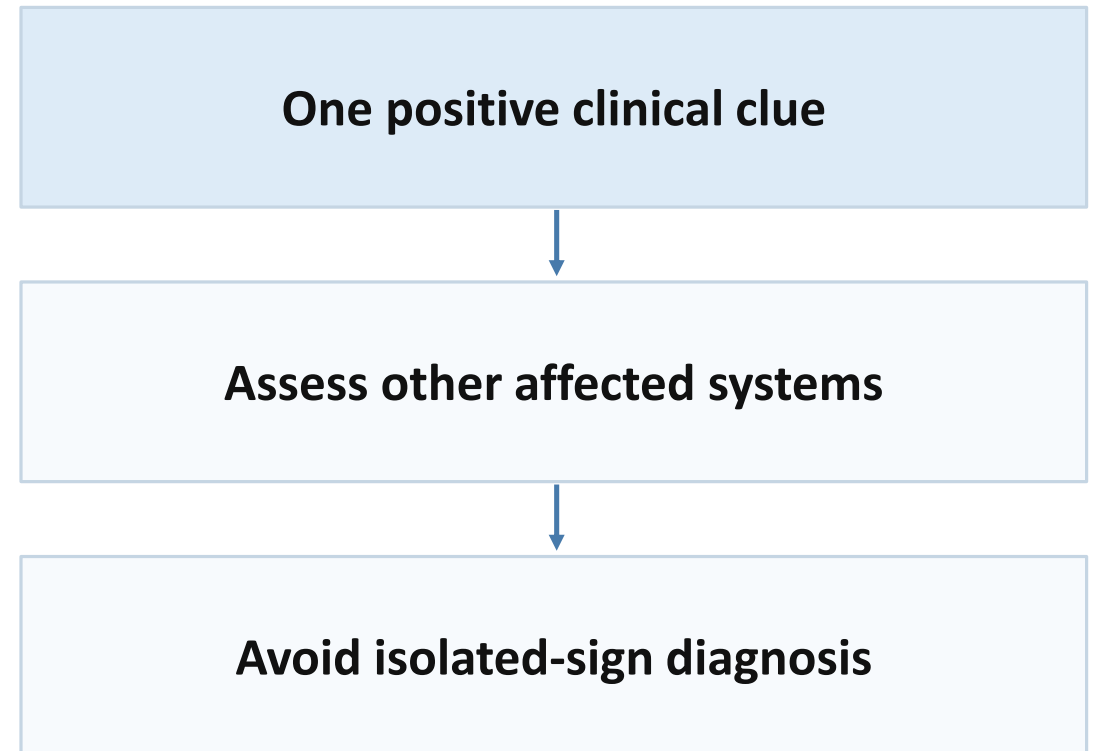
Expression varies within and between families

Type of variability	Meaning
Intrafamilial	Different features among relatives
Interfamilial	Different patterns among families
Mutation heterogeneity	Plausible contributor to variation

- The source describes variable manifestations within families
- Differences between families may be more marked

Absence of one organ-system sign cannot exclude disease

- Ocular abnormalities may occur without a striking skeletal phenotype
- Likewise, skeletal findings may be prominent without eye changes
- The clinical assessment should deliberately survey multiple systems



Schematic — causal sequence

Revised Ghent diagnosis integrates several evidence types

Family context	Clinical findings	Molecular evidence
Inheritance history	Aorta, lens and systemic signs	Relevant FBN1 variant

- The source names family history, cardinal clinical features, and FBN1 status
- Cardiovascular and ocular findings are particularly salient
- The textbook excerpt is not a complete operational list of diagnostic rules

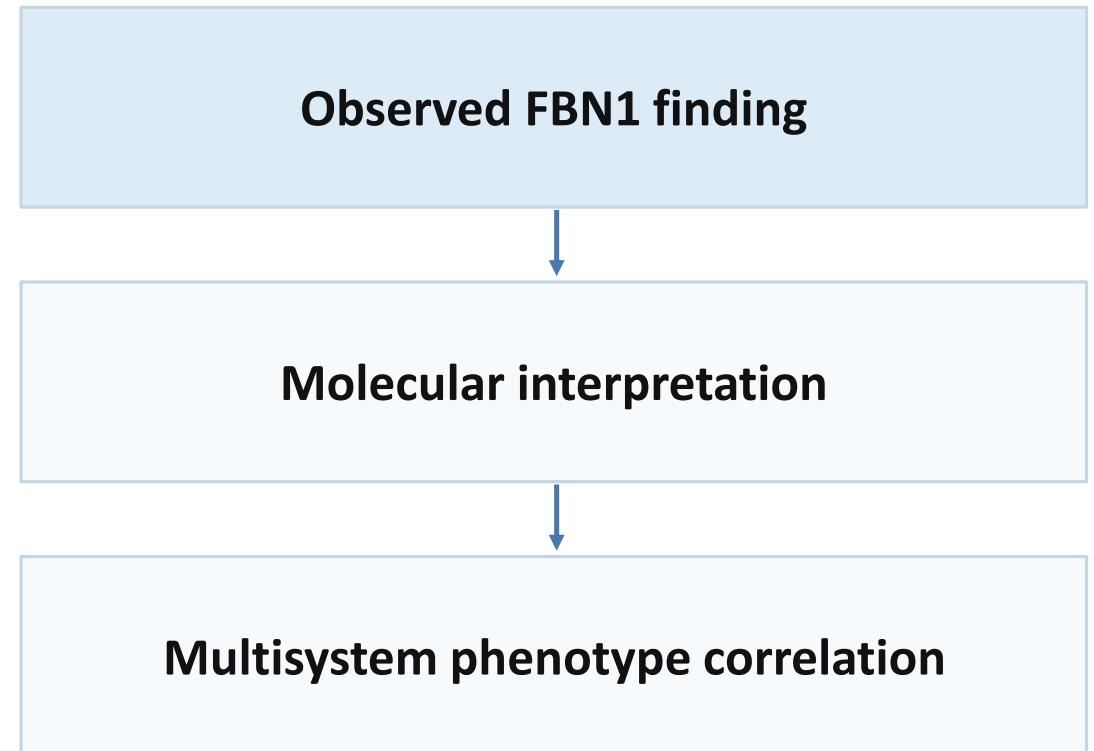
A diagnostic assessment requires separate organ-system observations

Skeletal examination	Ophthalmic examination	Cardiovascular assessment
Morphologic findings	Lens position	Aortic and valve findings

- Record skeletal features without equating them with diagnosis
- Seek ocular features such as ectopia lentis
- Determine cardiovascular abnormalities with appropriate clinical evaluation

A gene result is interpreted alongside the phenotype

- FBN1 variants are diverse in molecular effect
- The disease may involve dominant-negative action or haploinsufficiency
- A molecular observation and a compatible clinical phenotype together are more informative



Schematic — causal sequence

Marfan and Ehlers–Danlos syndromes target different matrix systems

Feature	Marfan syndrome	Ehlers–Danlos syndromes
Principal matrix defect	Fibrillin-1 / microfibrils	Collagen / collagen-related processes
Typical emphasis	Lens, skeleton and aorta	Skin, joints and tissue fragility

- Marfan syndrome involves fibrillin-rich microfibrils
- Ehlers–Danlos syndromes often involve collagen or collagen processing

FBN2-associated contractural arachnodactyly is not Marfan syndrome

Disorder	Associated gene	Teaching distinction
Marfan syndrome	FBN1	Multisystem fibrillin-1 disorder
Congenital contractural arachnodactyly	FBN2	Related but distinct skeletal disorder

- Both disorders affect proteins in the fibrillin family
- The source assigns congenital contractural arachnodactyly to FBN2

Case: Bilateral ectopia lentis with subtle skeletal changes

Finding: Bilateral ectopia lentis

- A patient has bilateral lens displacement and few obvious skeletal signs
- Which organ system must still be carefully assessed?

Answer: The cardiovascular system, particularly the aorta

Case: Marked arachnodactyly without known family history

Finding: Skeletal pattern; No family history

- A patient has long limbs, arachnodactyly, and chest-wall deformity
- Does an unaffected family history rule out Marfan syndrome?

Answer: No; Sporadic de novo variants are described

Case: Mitral prolapse should not end the evaluation

Finding: Mitral valve prolapse

- A patient has mitral valve prolapse in a connective-tissue phenotype
- What additional cardiovascular issue matters most?

Answer: Assess aortic involvement because of dissection risk

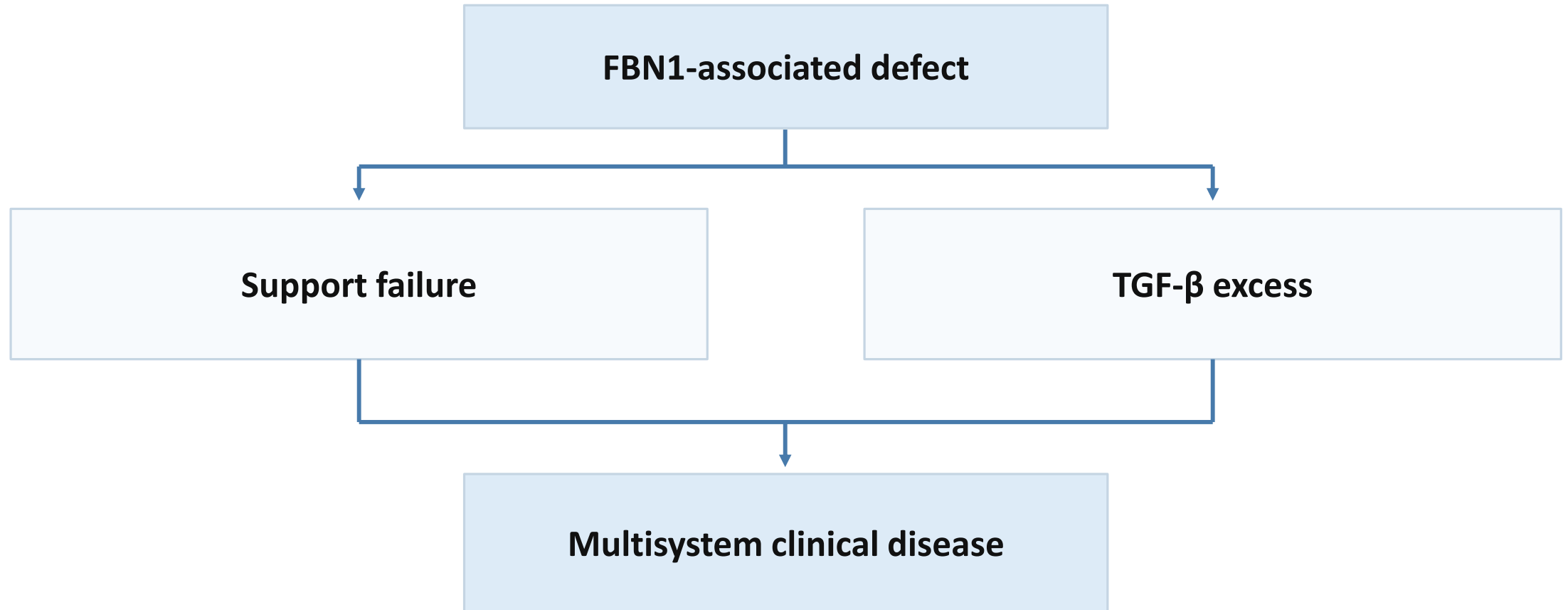
Case: A genotype must be explained mechanistically

Molecular clue: Abnormal fibrillin-1 disrupts assembly

- A variant produces abnormal fibrillin-1 that disrupts assembly
- Which dominant molecular mechanism does this exemplify?

Answer: Dominant-negative interference with microfibril formation

Mechanistic synthesis: Genotype to organ injury



FBN1 mutation produces abnormal quantity or quality of fibrillin-1

Schematic — dual disease mechanisms

Clinical synthesis: Recognize and prioritize

Recognition	Mechanism	Priority
Eyes and skeletal pattern	Microfibrils and signaling	Aortic assessment

- Ectopia lentis is a highly characteristic clue
- Skeletal findings help recognize the phenotype but vary greatly
- Aortic involvement is the central life-threatening concern

References and source boundaries

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th ed. (2026), Chapter 5, pp. 129–130
- Adjacent parent context: “Autosomal Dominant Disorders,” Chapter 5
- Adjacent Ehlers–Danlos section: comparison of extracellular-matrix disorders