

Inherited Diseases of Skeletal Muscle

Congenital myopathies

Congenital muscular dystrophies

Genotype, morphology, and clinical phenotype

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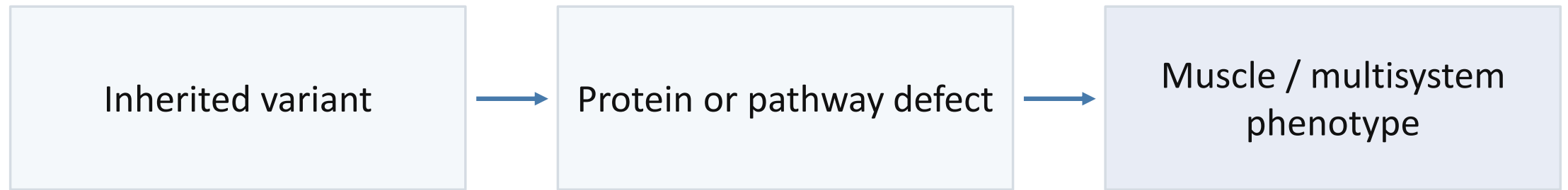
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Learning objectives

- Distinguish congenital myopathies from progressive muscular dystrophies.
- Associate RYR1, nemaline, and centronuclear disorders with structural signatures.
- Explain matrix and α -dystroglycan defects in congenital muscular dystrophy.
- Integrate inheritance, course, phenotype, and morphology.

Inherited myopathies form a heterogeneous disease spectrum



- Muscle dysfunction—with variable extracardiac and systemic involvement

Skeletal muscle may not be the only affected organ

Predominantly skeletal muscle

Muscle + other organs

Anatomic extent varies among inherited myopathies.

- Cardiac involvement is especially important because it may limit survival.

Clinical classification uses several independent axes

Inheritance / pedigree

Age of onset

Pattern of weakness

Course of disease

Biopsy / molecular mechanism

Major inherited skeletal-muscle disease categories

Group	Defining emphasis
Congenital myopathy	Structural abnormality; Often infancy onset
Muscular dystrophy	Progressive muscle injury
Congenital muscular dystrophy	Infancy onset + progressive injury
Channel / metabolic myopathy	Excitability or bioenergetics

Age at onset and disease course are not interchangeable

Congenital onset $\neq$ invariably progressive

Progression must be assessed separately

Use onset and trajectory as distinct diagnostic descriptors.

- Congenital muscular dystrophies generally combine early presentation with progressive injury.

Mechanism and muscle compartment shape phenotype

Sarcomere / Z-disk



Nemaline

Calcium-release system



Central core

Myonuclear localization



Centronuclear

Extracellular matrix

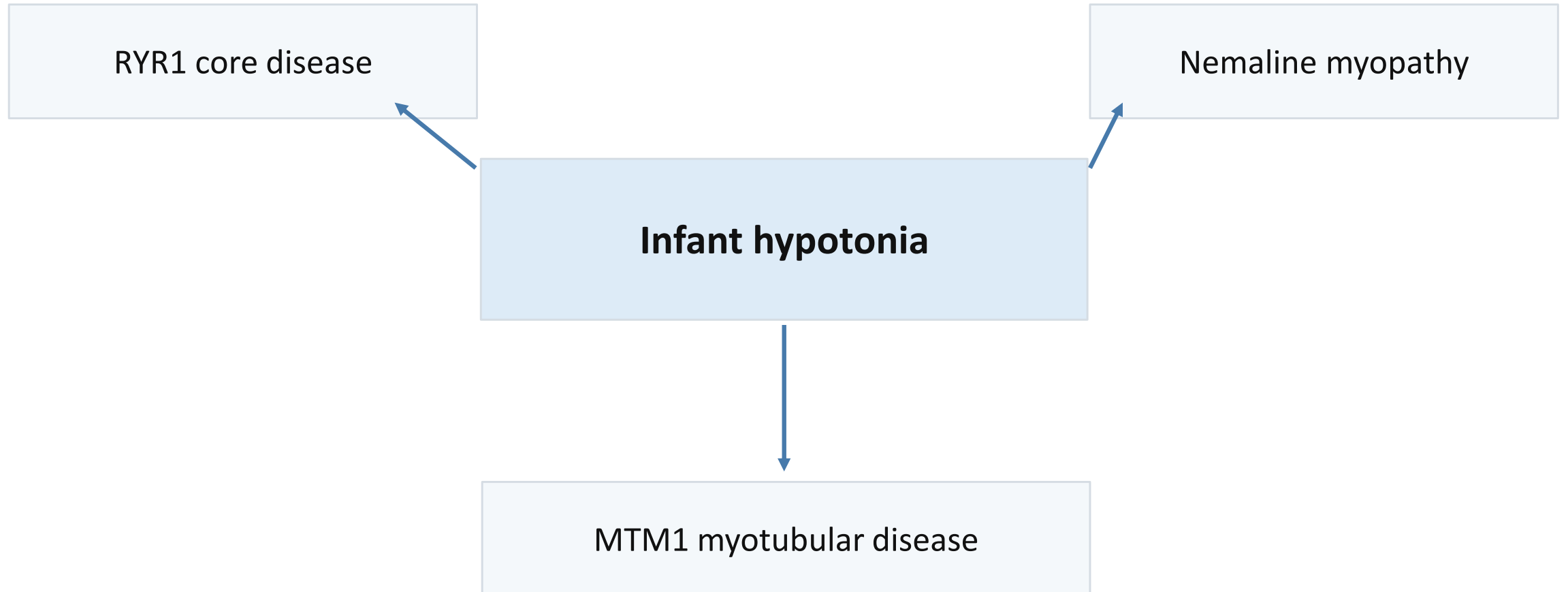


Congenital dystrophy

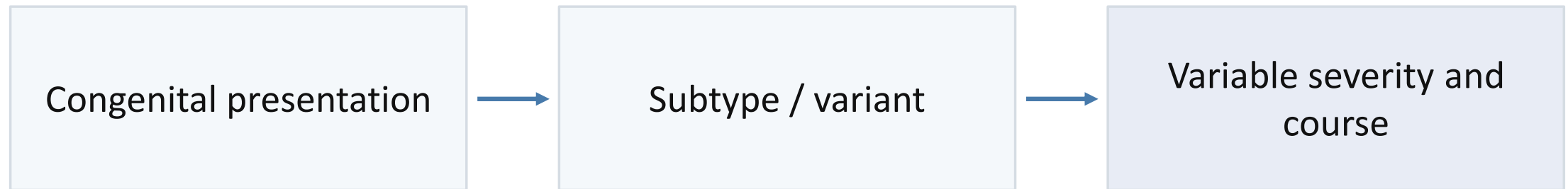
Congenital myopathy is primarily a structural concept

- Many affected infants present with hypotonia and weakness.
- Microscopy can reveal disease-defining alterations of fiber architecture.
- The structural diagnosis should be interpreted alongside a molecular diagnosis.

The “floppy infant” is a clinical presentation, not an etiologic diagnosis



Congenital myopathies have different natural histories



- Specific subtype and variant matter more than the umbrella label alone.

Central core disease is linked to RYR1

RYR1

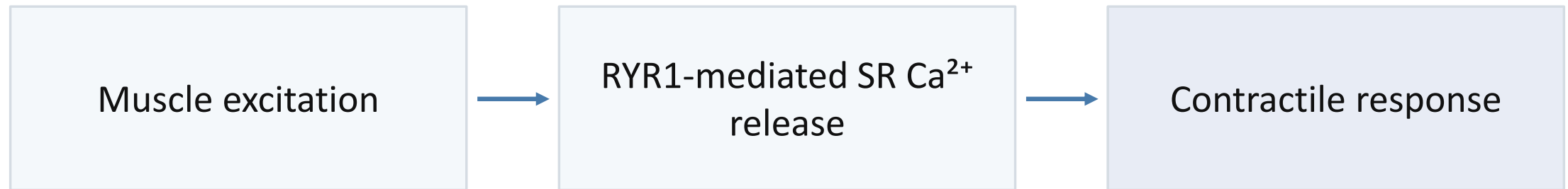


Central core disease

Autosomal dominant (table example)

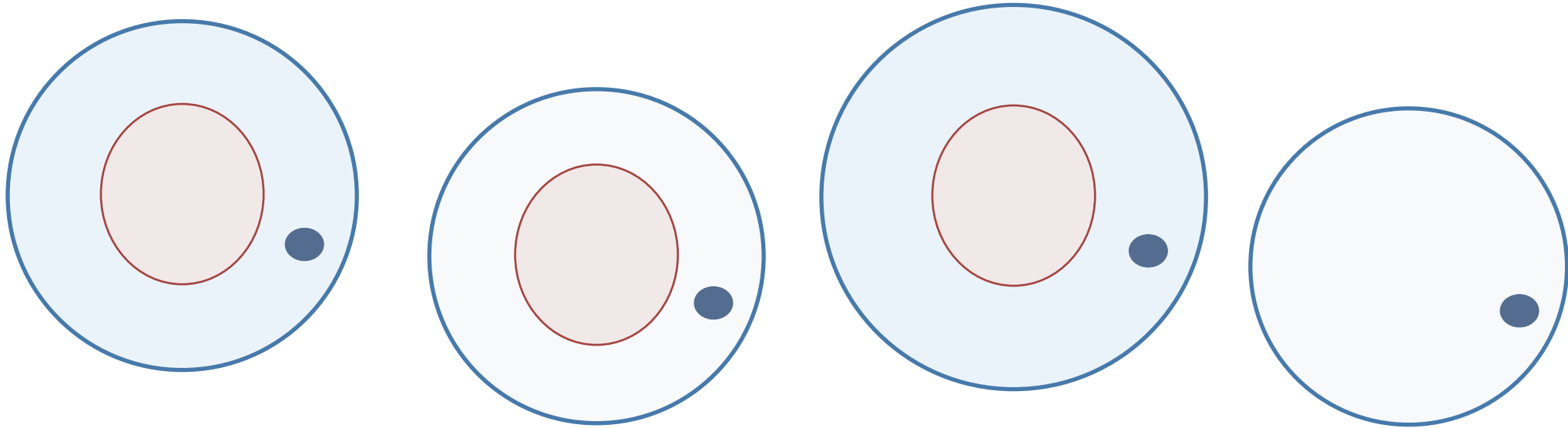
- The disorder may appear as early hypotonia and weakness.

RYR1 couples excitation to intracellular calcium release



- Disrupted calcium handling impairs coordinated contraction.

The “central core” is a myofiber architectural lesion



Dashed core zones: Disrupted sarcomeres and reduced mitochondria.

Schematic — conceptual cross-sections, not a patient biopsy.

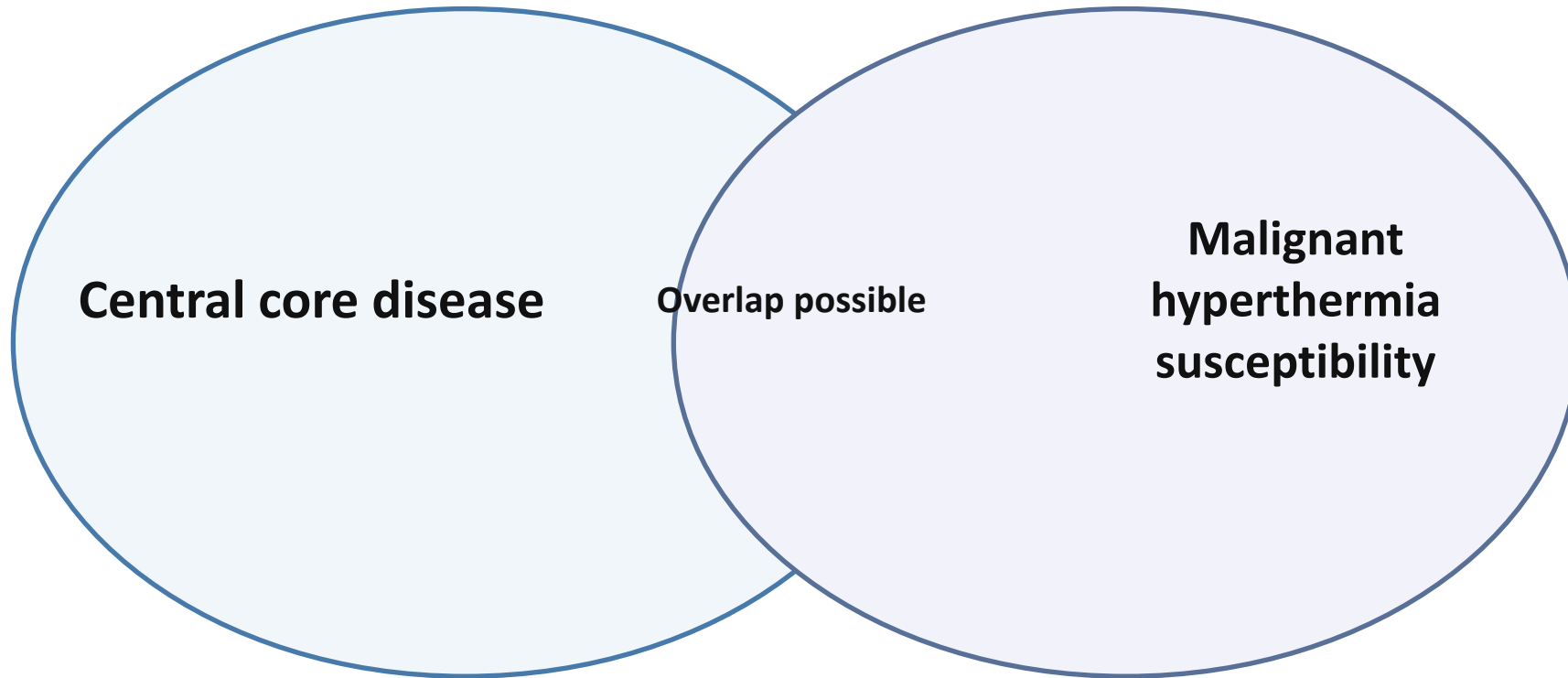
Central cores combine contractile and mitochondrial abnormalities

Outside the core	Within the core
Organized sarcomeres	Disorganized sarcomeres
Usual mitochondria	Fewer mitochondria
Recognizable fiber architecture	Sharply demarcated central region

Central core disease may affect the skeleton as well as muscle

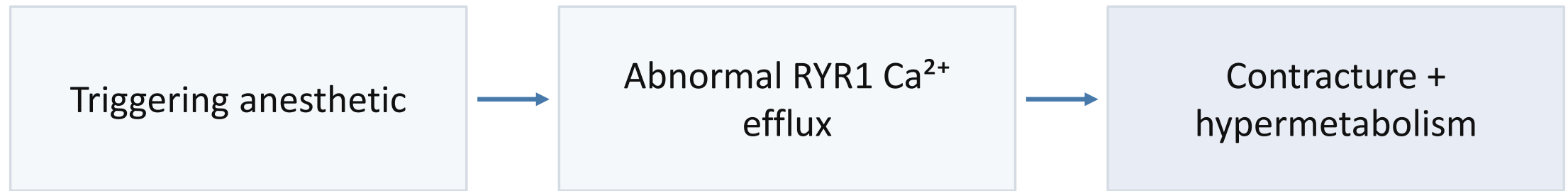
- Early-onset hypotonia and weakness are typical table entries.
- Associated skeletal changes may include scoliosis.
- Hip dislocation and foot deformities are also described.

RYR1 variants produce overlapping disease phenotypes



- Some variants are associated with both phenotypes.

Malignant hyperthermia is a relevant RYR1 safety association



Context from the adjacent channelopathy section.

Nemaline myopathy is a genetically heterogeneous congenital myopathy

- Robbins Table 27.3 lists multiple sarcomere-related genes.
- Patients may have childhood weakness or severe hypotonia at birth.
- A common pathologic descriptor is the presence of nemaline rods.

Nemaline disease implicates several contractile proteins

TPM3

TPM2

NEB

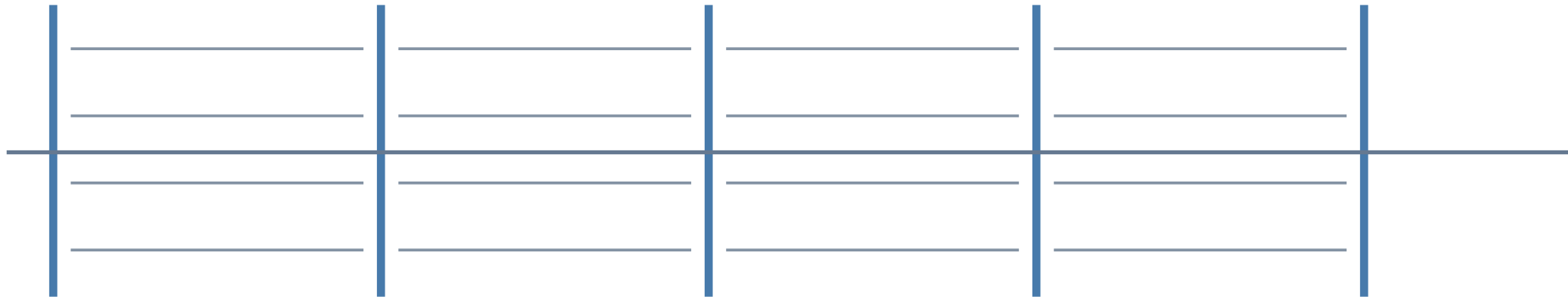
ACTA1

TNNT1

CFL2

- A single “nemaline gene” does not explain this morphologic group.

Nemaline rods are derived from Z-band material

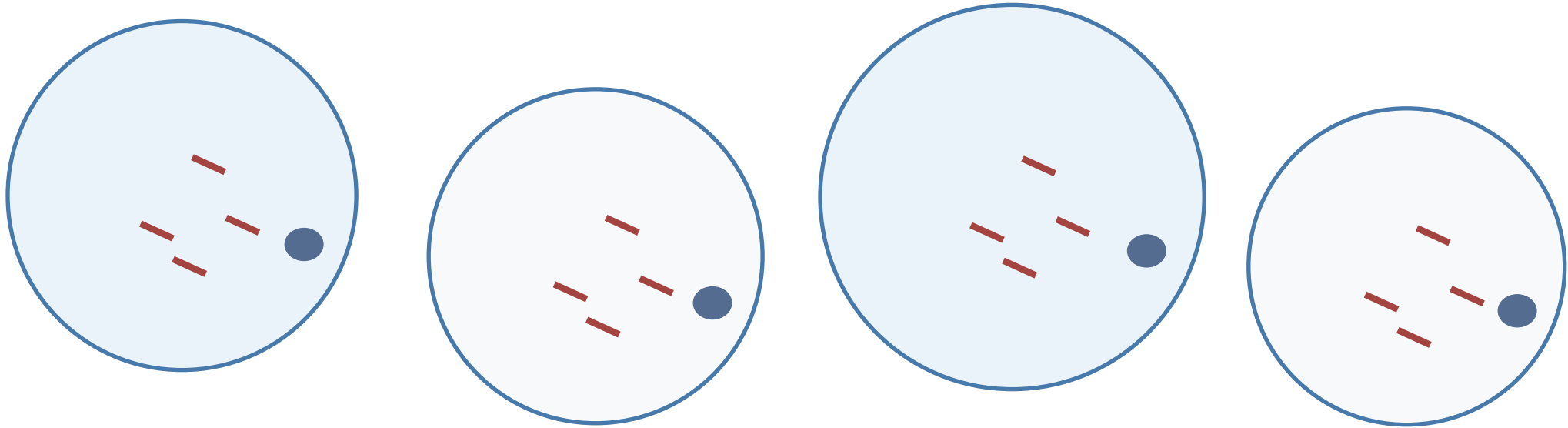


Z-disk-associated material



Nemaline rod aggregates

Nemaline rods have characteristic shape and fiber distribution



Red short rods: Z-band–derived nemaline aggregates.

Schematic — conceptual cross-sections, not a patient biopsy.

Nemaline clinical severity varies

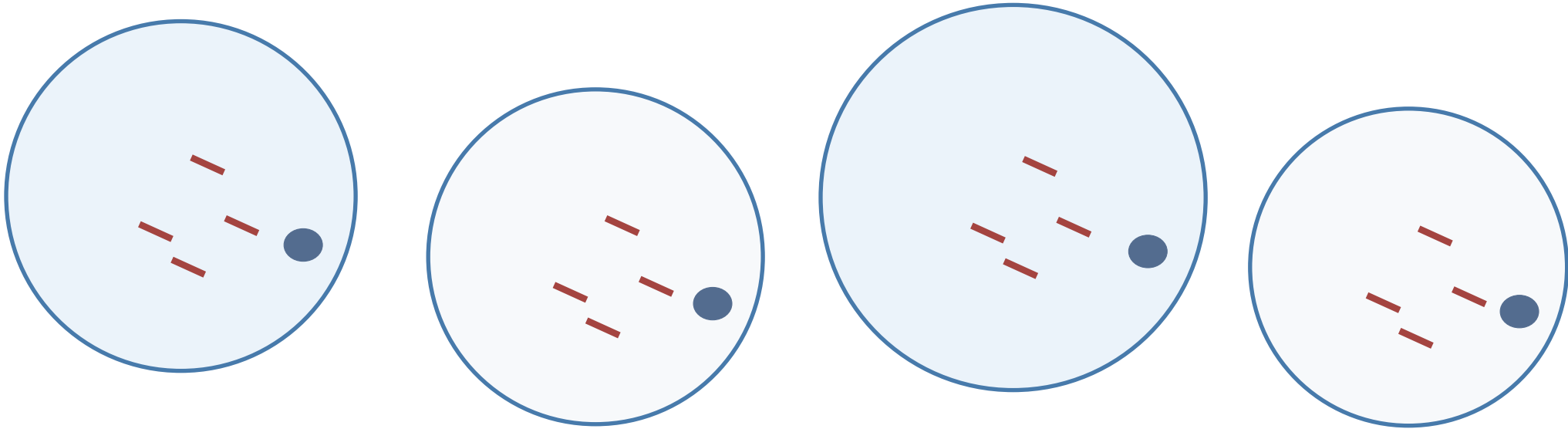
Infancy: Hypotonia may be severe

Childhood: Persistent weakness

Variable presentations within a shared rod-myopathy morphology.

- The clinical spectrum is broader than any one gene–phenotype pairing.

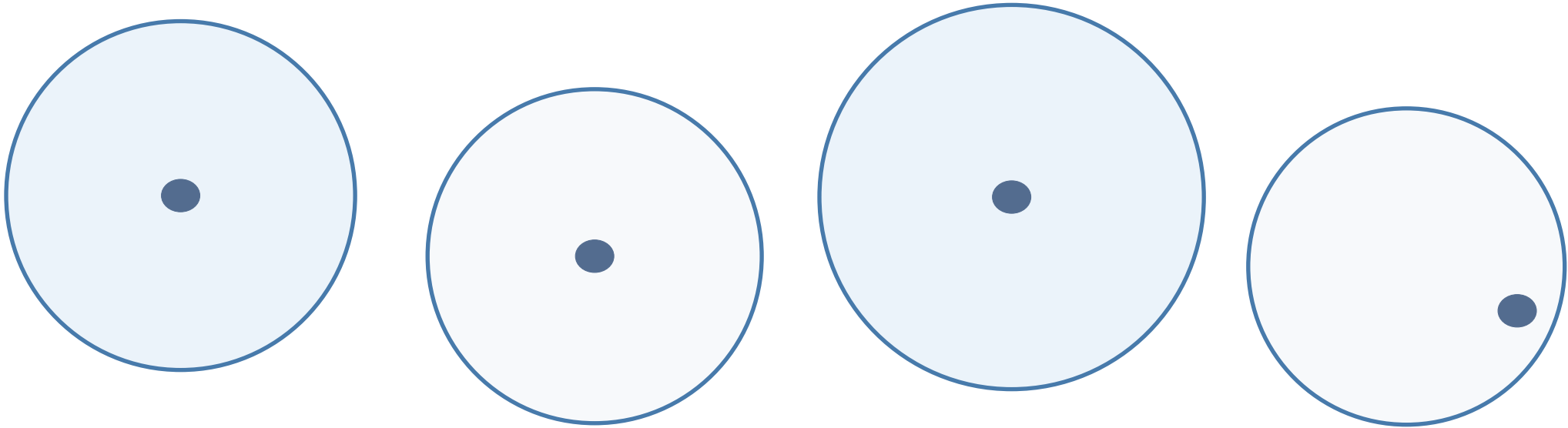
Nemaline rods require appropriate structural visualization



Red short rods: Z-band–derived nemaline aggregates.

Schematic fiber only — not an authentic stained section.

Centronuclear myopathy features misplaced myonuclei



Blue nuclei positioned centrally in most modeled fibers.

Schematic — conceptual cross-sections, not a patient biopsy.

Normal myonuclei provide the comparison standard

Expected mature fiber	Centronuclear phenotype
Peripheral myonuclei	Many centrally situated nuclei
Normal size distribution	Often small type I fibers
Nuclear location not dominant	Nuclear pattern is characteristic

X-linked myotubular myopathy is associated with MTM1

MTM1



Myotubular myopathy

X-linked

- A poor prognosis in the severe X-linked form.

Autosomal dominant centronuclear disease can involve DNM2

DNM2



Centronuclear myopathy

Autosomal dominant

- Weakness and hypotonia remain central clinical features.

Autosomal recessive centronuclear disease can involve BIN1

BIN1

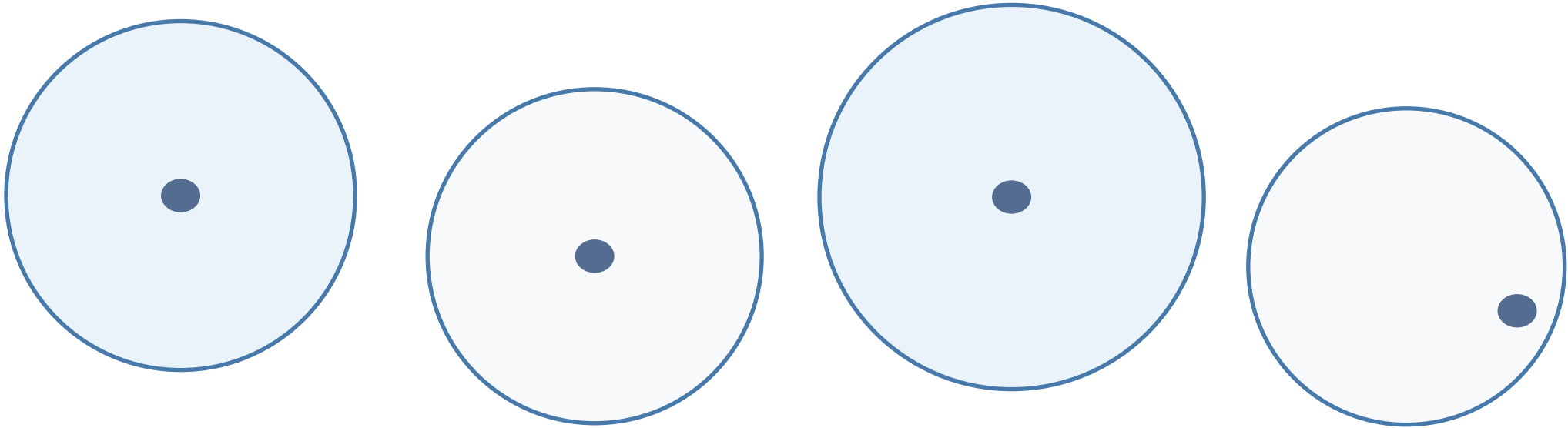


Centronuclear myopathy

Autosomal recessive

- Clinical course and presentation differ from severe MTM1-associated disease.

Type I fibers may be small in centronuclear myopathy



Blue nuclei positioned centrally in most modeled fibers.

Schematic fiber-type relationship; Not a biopsy.

Central nuclei alone do not establish a molecular diagnosis

Centronuclear myopathy

Many central myonuclei as core phenotype

Subtype-specific gene correlation

Family history supports inheritance

Nonspecific myopathic regeneration

Internal nuclei can accompany repair

Necrosis/regeneration context

Other acquired causes are possible

Structural signatures distinguish three congenital myopathies

Central core

Core zones

RYR1

Nemaline

Rod inclusions

Multiple sarcomeric genes

Centronuclear

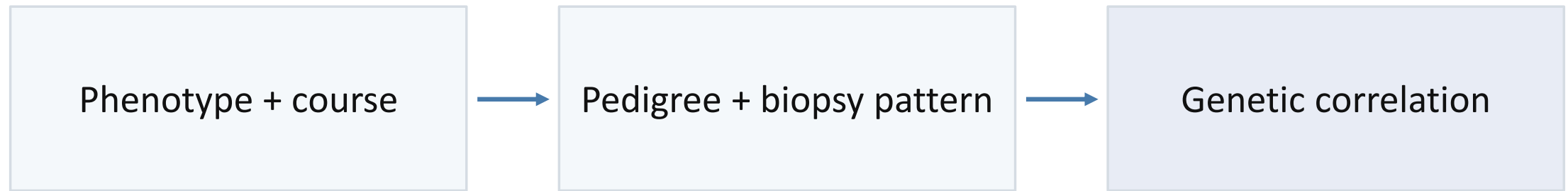
Central myonuclei

MTM1 / DNM2 / BIN1

Inheritance patterns narrow the congenital myopathy differential

Phenotype	Textbook gene examples	Inheritance
Central core	RYR1	AD
Nemaline rods	TPM3 / NEB / ACTA1 and others	AD or AR
Centronuclear	MTM1 / DNM2 / BIN1	XL / AD / AR

A structural myopathy work-up integrates four domains



- Molecular analysis can establish the specific etiology.

Case 1: Neonatal hypotonia with central core morphology

- An infant has generalized hypotonia and weakness.
- Biopsy is reported to contain sharply defined central areas with disrupted sarcomeres and fewer mitochondria.
- Which gene and additional safety association should be considered?

Formulate the most likely mechanistic diagnosis before revealing the discussion.

Case 2: Marked central nuclei in many fibers

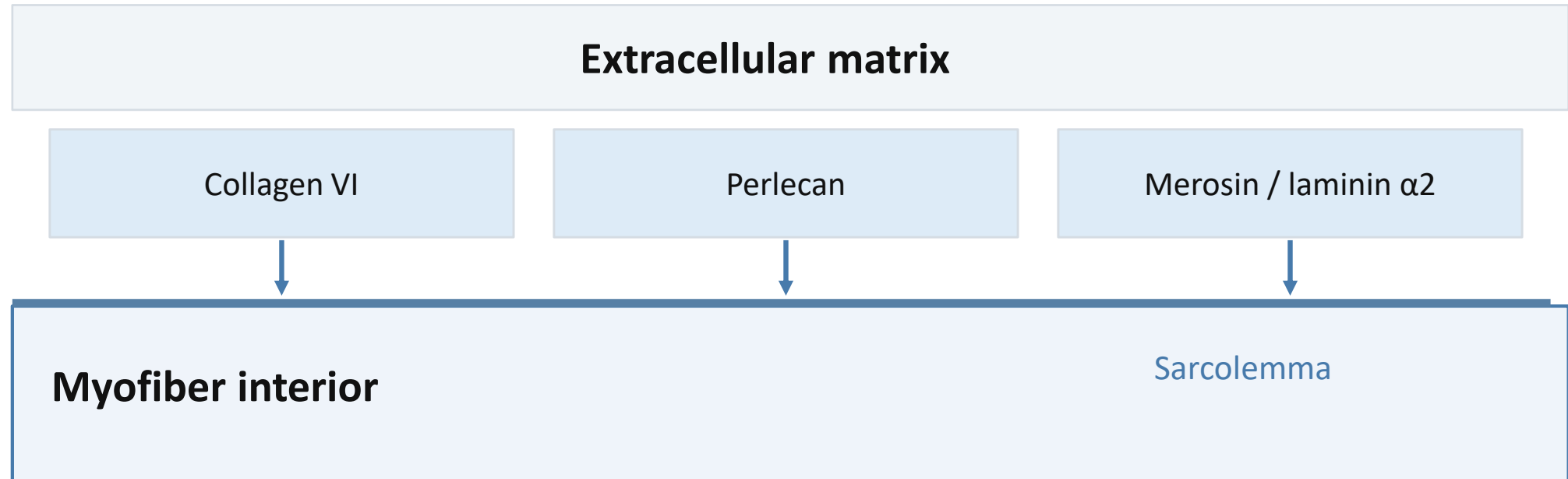
- A male newborn develops profound hypotonia.
- Numerous small muscle fibers show nuclei in the geometric center.
- Which congenital myopathy and gene fit this pattern?

Formulate the most likely mechanistic diagnosis before revealing the discussion.

Congenital muscular dystrophies combine early onset and ongoing injury

- These conditions present in infancy.
- Unlike structurally defined, relatively static congenital myopathies, progressive damage is a key feature.
- Developmental abnormalities of the central nervous system may accompany muscle disease.

Myofiber–matrix attachments are necessary for tissue integrity



Schematic of the myofiber–matrix interface

Congenital muscular dystrophy has two matrix-related routes

Matrix protein deficiency

Matrix receptor dysfunction

Distinct molecular lesions can converge on impaired attachment.

- Both routes disturb the myofiber–surrounding matrix interface.

Ullrich congenital muscular dystrophy is a collagen VI disorder

Collagen VI



Ullrich congenital muscular dystrophy

Extracellular-matrix defect

- Its phenotype combines weakness/hypotonia with joint abnormalities.

Ullrich congenital muscular dystrophy has a characteristic joint pattern

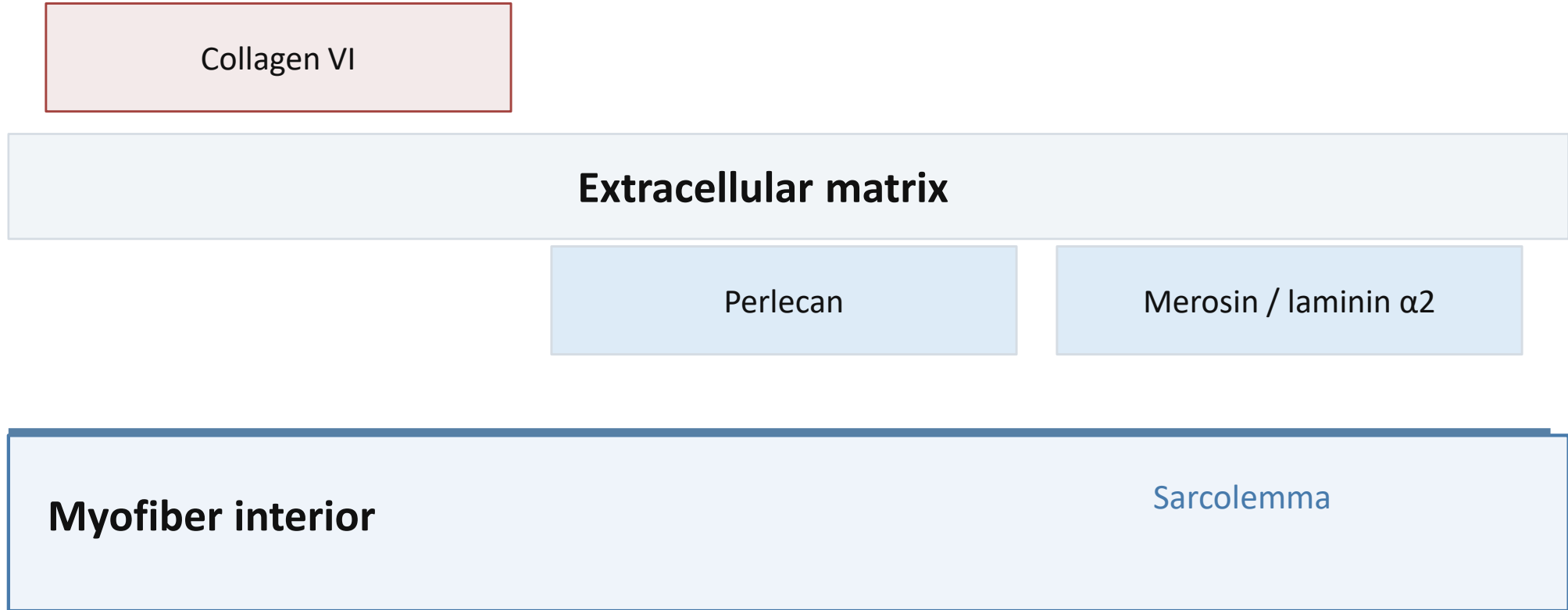
Proximal joint contractures

Distal joint hyperextensibility

Both can coexist in Ullrich congenital muscular dystrophy.

- Hypotonia accompanies the muscle disorder.

Collagen VI and perlecan lose their normal spatial association in Ullrich disease



Schematic of the myofiber–matrix interface

Matrix components are separated in Ullrich disease.

Merosin deficiency reflects disruption of LAMA2

LAMA2

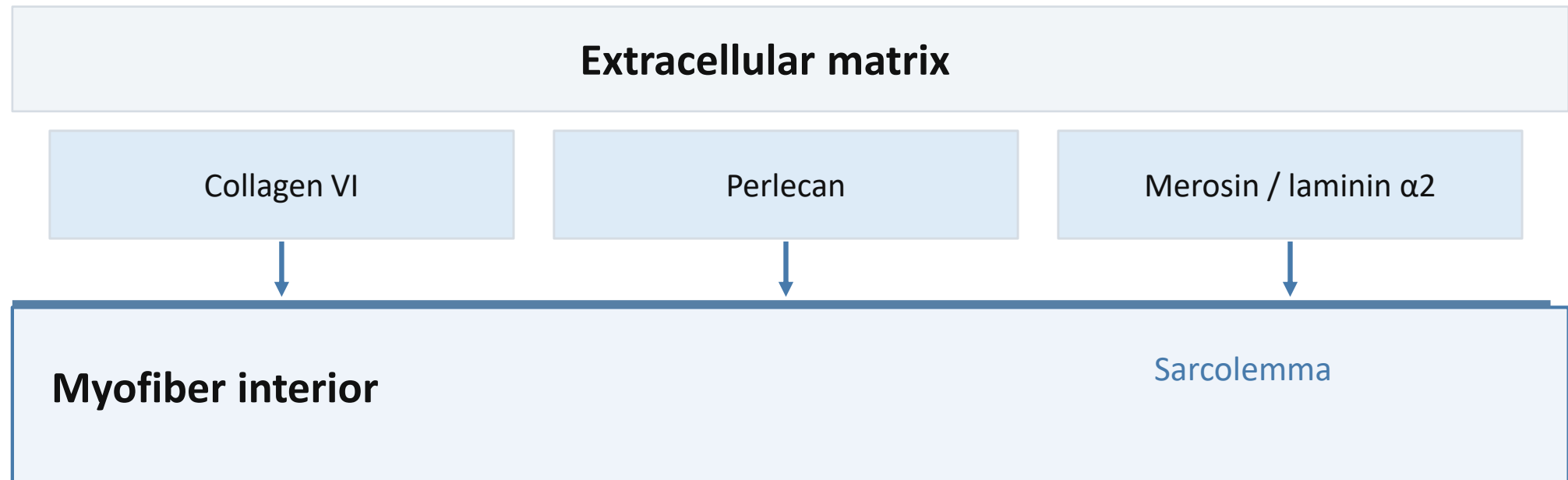


Merosin-deficient congenital muscular
dystrophy

Matrix-protein defect

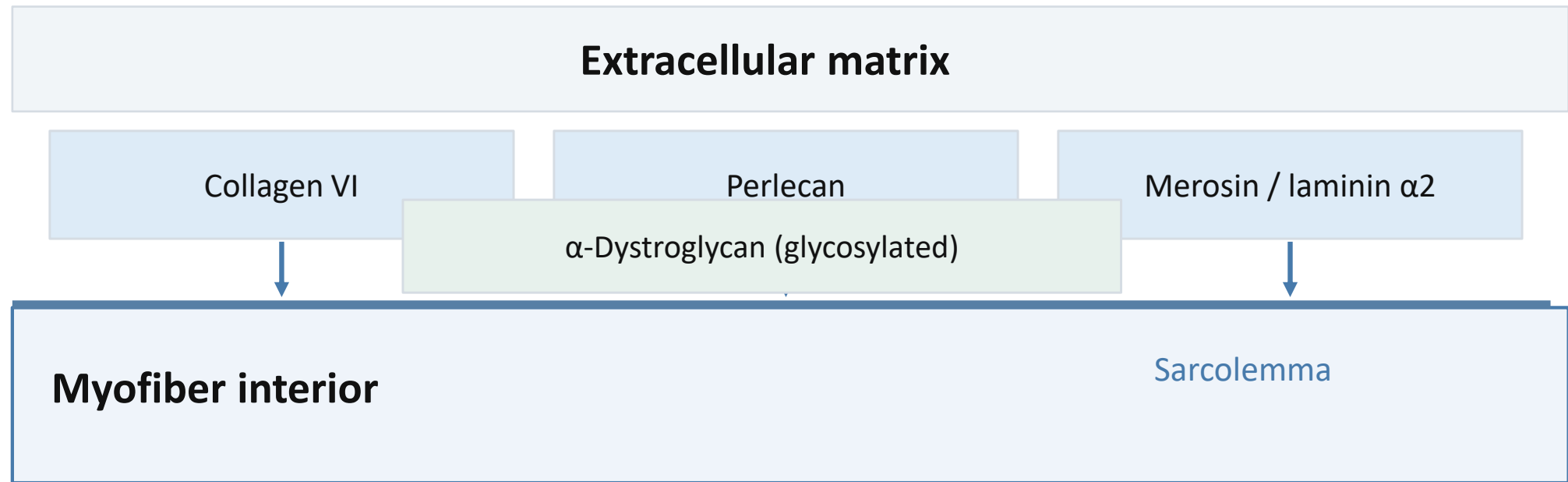
- A defective matrix component causes a congenital muscular dystrophy phenotype.

Laminin $\alpha 2$ is part of the myofiber's extracellular support



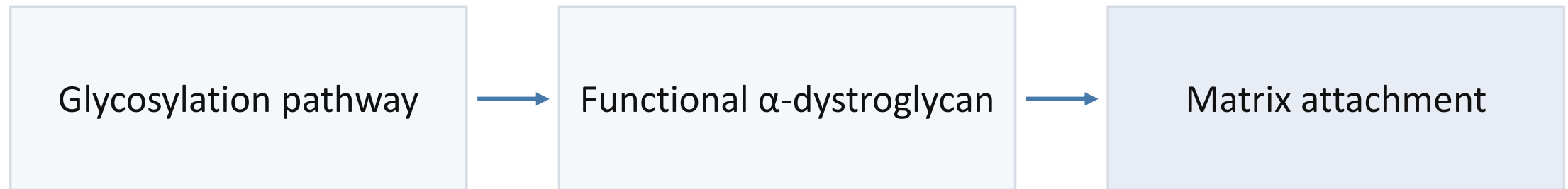
Schematic of the myofiber–matrix interface

α -Dystroglycan is a matrix-facing receptor component



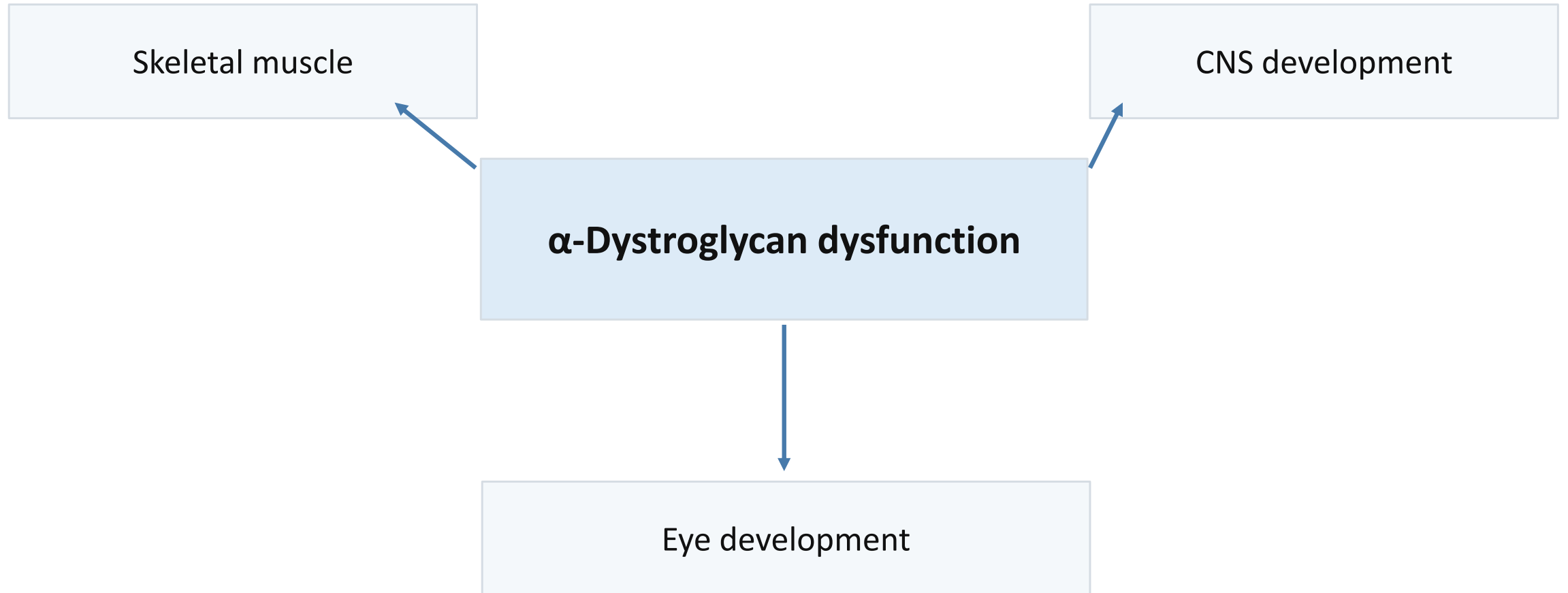
Schematic of the myofiber-matrix interface

O-linked glycosylation enables normal α -dystroglycan function

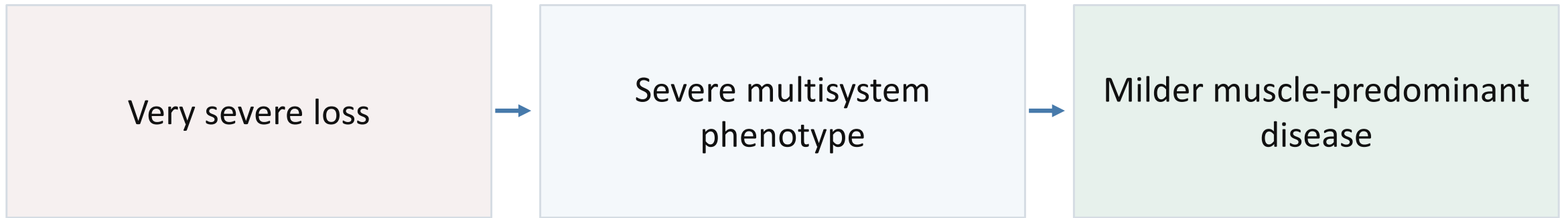


- A biochemical processing defect can therefore manifest as congenital muscular dystrophy.

Dystroglycanopathy may involve muscle, brain, and eye



Residual functional impairment helps explain disease severity



- The phenotypic range extends from severe multisystem disease to muscle-predominant forms.

Some dystroglycan defects overlap with limb-girdle dystrophy

Congenital dystrophy phenotype

Limb-girdle dystrophy phenotype

Shared pathway does not guarantee identical clinical onset.

- Classification follows the phenotype and course as well as the molecular pathway.

Congenital dystrophy: Three molecular-pathologic comparisons

Disease mechanism	Affected feature	Helpful clue
Collagen VI (Ullrich)	Extracellular matrix	Proximal contractures, distal hyperextensibility
LAMA2 (merosin)	Extracellular-matrix laminin	Congenital dystrophy
α -DG glycosylation	Matrix receptor processing	Variable CNS / ocular abnormalities

Congenital myopathy and congenital dystrophy should not be conflated

Feature	Congenital myopathy	Congenital muscular dystrophy
Unifying clue	Core, rod, or nuclear pattern	Progressive muscle damage
Typical onset	Often infancy	Infancy
Systemic findings	Variable by subtype	CNS / eye possible in select forms
Disease course	May be relatively static or severe	Usually progressive

Progressive muscular dystrophy usually appears beyond infancy

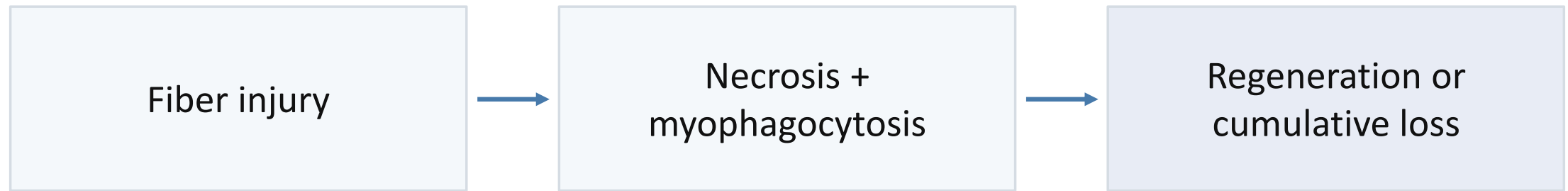
Congenital muscular dystrophy: Infancy

Other muscular dystrophies: Often later

Timing is informative but does not replace molecular classification.

- Congenital muscular dystrophies are the infancy-onset exception to this clinical pattern.

Dystrophic injury can overwhelm regenerative capacity



- Over time, repeated injury may exceed regenerative capacity.

Chronic dystrophy remodels muscle architecture



- Marked fiber-size variation reflects ongoing injury, loss, and adaptation.

Clinical progression and fiber pathology should be interpreted together

Structural congenital myopathy

Core / rod / centronuclear signature

May be relatively static

Genotype clarifies subtype

Progressive dystrophy

Necrosis and regeneration

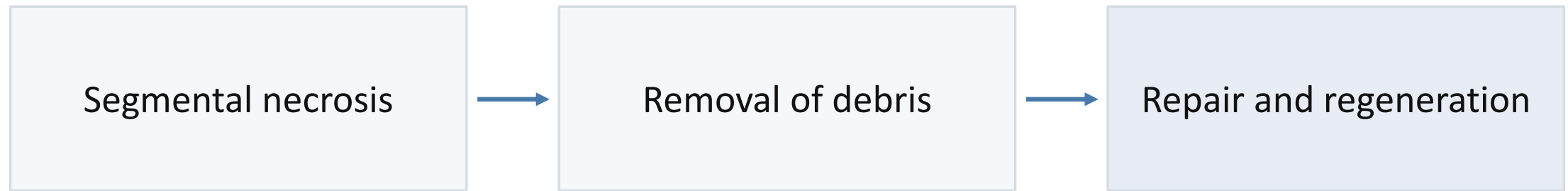
Accumulating tissue loss

Genotype confirms disease group

Serum creatine kinase indicates damage, not a specific genotype

- Damaged fibers release creatine kinase into blood.
- CK elevation can accompany dystrophic muscle injury.
- Interpret the value with weakness distribution, age, biopsy and molecular data.

Myopathic regeneration can complicate morphology



- Therefore an isolated internal nucleus cannot identify MTM1, DNM2, or BIN1 disease.

A structured inherited-myopathy assessment reduces category errors

Inheritance / pedigree

Age of onset

Pattern of weakness

Course of disease

Biopsy / molecular mechanism

Not every inherited myopathy is captured by these three groups

Related group	Dominant concept
Channelopathy	Muscle excitability / ion channels
Lipid or glycogen metabolism	Energy substrate handling
Mitochondrial myopathy	ATP generation / mitochondrial genetics

Case 3: Contractures with distal hyperextensibility

- An infant has hypotonia and proximal joint contractures.
- Examination also shows marked distal joint hyperextensibility.
- Which extracellular-matrix protein family best fits this combination?

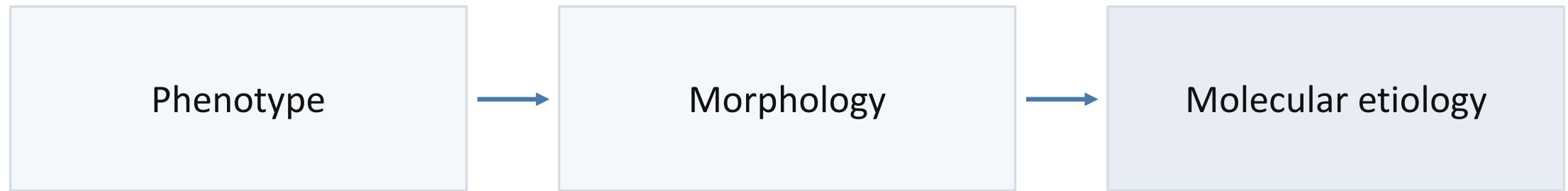
Formulate the most likely mechanistic diagnosis before revealing the discussion.

Case 4: Congenital dystrophy with eye and brain anomalies

- An infant has progressive muscle weakness and developmental abnormalities affecting the brain and eyes.
- The suspected lesion impairs posttranslational modification of a matrix receptor.
- Which receptor-associated pathway should be prioritized?

Formulate the most likely mechanistic diagnosis before revealing the discussion.

Integrate phenotype, lesion, and inheritance in the final diagnosis



- Genetics links these phenotypes to RYR1, sarcomeric genes, MTM1/DNM2/BIN1, matrix genes, or glycosylation pathways.

Core distinctions to retain

- Core + RYR1: Consider a variant-dependent malignant hyperthermia association.
- Nemaline rods: Sarcomeric/Z-band phenotype with genetic heterogeneity.
- Central nuclei: MTM1, DNM2, or BIN1 depending on inheritance and course.
- Congenital dystrophy: Matrix or receptor dysfunction; Some forms involve brain and eye.

Selected textbook source

- Robbins, Cotran & Kumar: Pathologic Basis of Disease, 11th edition (2026).
- Inherited Diseases of Skeletal Muscle, Chapter 27.
- Contextual passages: Myopathic Changes; Muscular Dystrophies; Ion Channel Myopathies; Mitochondrial Myopathies.